SYNTHESIS, CHARACTERIZATION OF SOME NOVEL 2-BUTYL 3-SUBSTITUTEDAMINO QUINAZOLIN 4(3H)-ONES AND EVALUATION OF ANTICONVULSANT AND ANALGESIC ACTIVITIES

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in partial fulfillment of the requirements for the
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MADURAI MEDICAL COLLEGE,
MADURAI-625 020.

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College of Pharmacy,
Madurai Medical College,
Madurai.

CERTIFICATE

This is to certify that the dissertation entitled **"SYNTHESIS, CHARACTERIZATION OF SOME NOVEL 2-BUTYL-3-SUBSTITUTED QUINAZOLIN-4(3H)-ONES AND EVALUATION OF ANTI CONVULSANT AND ANALGESIC ACTIVITIES"** was carried out by **Miss.V.Umamaheswari**, in the Department of Pharmaceutical Chemistry, Madurai Medical College, Madurai-625 020, in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmaceutical Chemistry under my guidance and supervision during the academic year 2009-2010.

This dissertation is forwarded to The Controller of Examinations, The Tamil Nadu Dr.M.G.R Medical University, Chennai.

Station: Madurai (**Mrs.R.THARABAI**)

Date:

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I extend my thanks to all my **PG friends** of Pharmaceutics and Pharmacognosy for their help and support.

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I deem it my great privilege to be able to acknowledge all those eminent personalities, who helped me throughout this endeavor.

CONTENTS

INTRODUCTION

Drug discovery has its beginning in the root of mankind. Medicinal chemistry is a science whose roots lie in all branches of chemistry and biology[1].

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease[2]. The recent advancement like drug designing, combinatorial chemistry, molecular biology and genetic engineering make interesting the medicinal chemistry approach[3].

Modern Drug Design, as compared with," Let's make a change on an existing compound or synthesis a new structure and see what happen" is a fairly recent discipline still in its infancy.

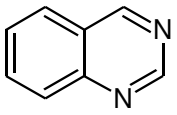
Early Drug Design started with elucidation of the structure of the natural product, followed by selective changes in the molecule. The later was done for many reasons, including the reduction of an undesirable pharmacological response (side effects), obtaining a better pharmacokinetic response, altering the drug's metabolism, securing a more plentiful, less costly supply and producing a competing product[2].

Once a new Pharmaceutical Lead Compound has been identified, extensive and costly efforts usually are made to prepare a series of analogue in the hope that even better activity will be found[2].Medicinal chemistry remains a challenging science which provides profound satisfaction to its practioners[4].

Medicinal Chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby contribute to a healthier and happier life[5].

QUINAZOLINONES- AN OUTLOOK

Quinazoline is a fused bicycle compound earlier known as benzo 1, 3 diazine was first prepared in the laboratory by Gabriel in 1903 [6, 55]

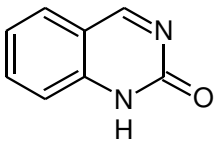


quinazoline

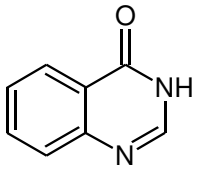
The name Quinazoline was first proposed for this compound by Weddige on observing that this was isomeric with the compounds cinnoline and Quinoxaline.

Depending upon the position of the keto (or) oxo group, these compounds may be classified in to two types:

1. 2-(1H) Quinazolinone
2. 4-(3H) Quinazolinone



quinazolin-2(1*H*)-one



quinazolin-4(3*H*)-one

Due to the broad spectrum of biological properties of derivatives of Quinazolinone their synthesis has been a focus of significant interest in recent years.

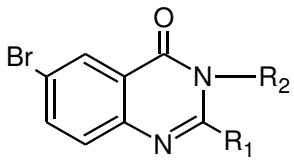
The structure activity relationship studies of Quinazolinone ring system revealed in various Literatures suggests position 2, 6 and 8 are very much important for structure activity studies and position 3 should be attached to different heterocyclic rings for better chemotherapeutic activity.

Of the various Quinazolines reported, the C-2 and N-3 disubstituted Quinazolines exhibited interesting pharmacological activities like analgesic, anti inflammatory, anticonvulsant, antibacterial activities, etc [7].

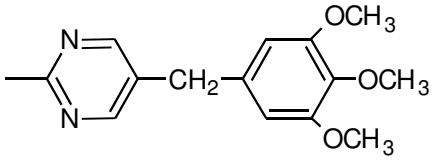
From the review of various Literatures, it was known that Quinazolin-4-ones have emerged as an important class of nitrogenated Heterocycles that have attracted significant synthetic interest because of their therapeutic and Pharmacological properties such as antibacterial, antifungal, anthelmintic, anti-inflammatory, anticonvulsant, CNS depressant, hypoglycemic, antiparkinsonian, anticancer, antiviral, antihistaminic, antihypertensive, analgesic and many other activities.

REVIEW OF LITERATURE

1. **Murugesan Dinakaran et al.,** synthesized 6-bromo-2, 3 disubstituted 4-(3H)-Quinazolinones and evaluated the antiviral & cytotoxic activity.[8]

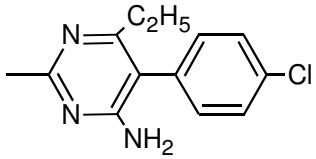


(i) $R_1 = CH_3$ $R_2 =$

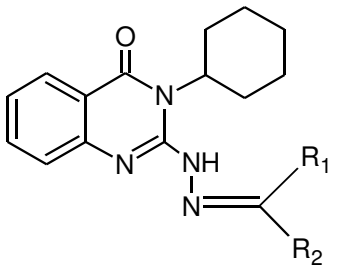


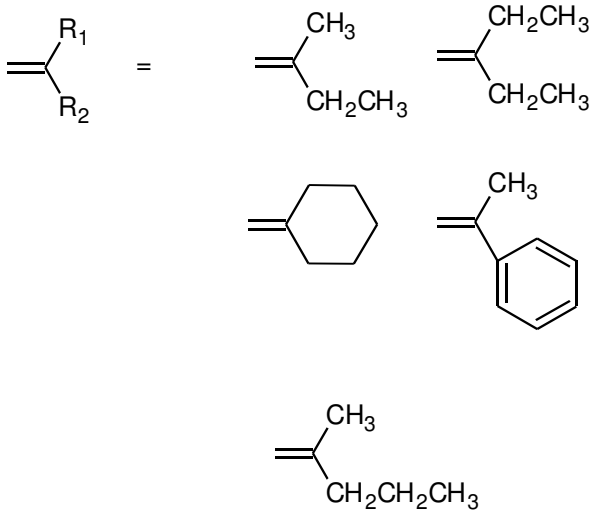
(ii) $R_1 = C_6H_5$

$R_2 =$

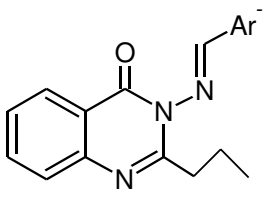


2. **Veerachamy Alagarsamy et al.,** synthesized 3-cyclohexyl-2-substituted hydrazino-3H-Quinazolin-4-ones as analgesic and anti-inflammatory agents.[9]





3. A.M.F Eissa et al., synthesized 2-propyl 4(3H)-Quinazolinone derivatives as antibacterial agents.[10]

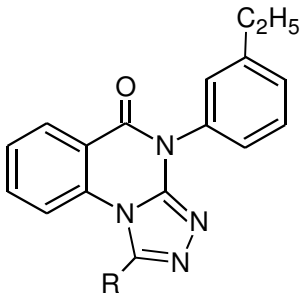


Ar = 3, 4 $C_6H_3(OCH_3)_2$

Ar = 4 C_6H_4 $N(CH_3)_2$

Ar = 3, 4 $C_6H_30_2CH_2$

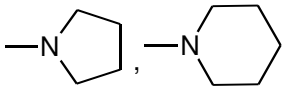
4. **Veerachamy Alagarsamy et al.,** synthesized novel 4-(3-ethyl phenyl)-1-substituted-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-ones as a new class of H1- antihistaminic agents.[11]



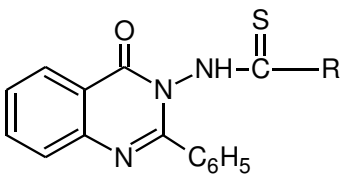
R= -SH, -SCH_3, $NHNH_2$, -H,

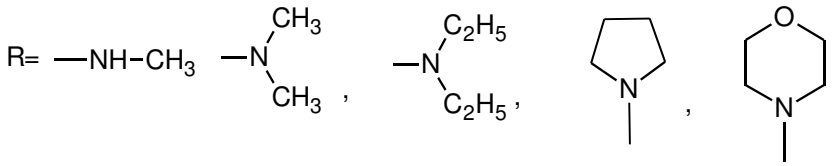
-CH_3, -CH_2CH_3,

-$(CH_2)_2$ CH_3, -CH_2Cl,

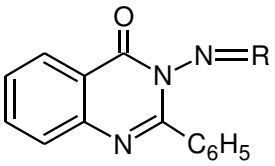


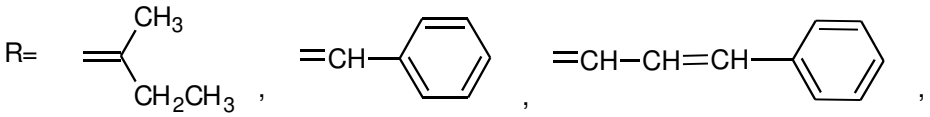
5. **Veerachamy Alagarsamy et al.,** synthesized novel -2 phenyl 3-substituted Quinazolin-4(3H)ones as analgesic, anti-inflammatory & antibacterial agents.[12]

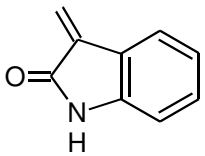




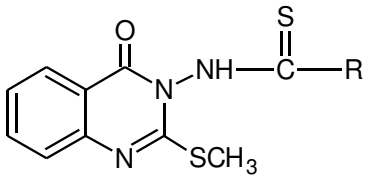
6. **Veerachamy Alagarsamy et al.,** synthesized novel -2, 3-Disubstituted Quinazolin-4(3H)ones as analgesic & anti-inflammatory agents.[13]

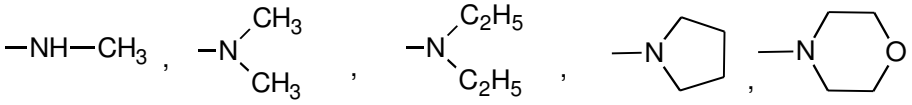




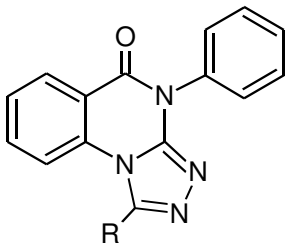


7. **Veerachamy Alagarsamy et al.,** synthesized novel -2 methyl thio 3-substituted Quinazolin-4(3H)ones as analgesic, anti-inflammatory & antibacterial agents.[14]



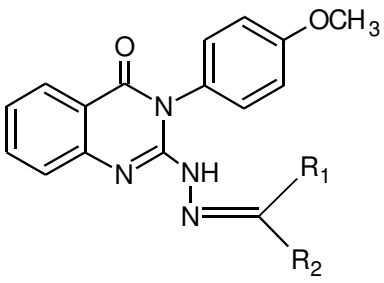
R= 

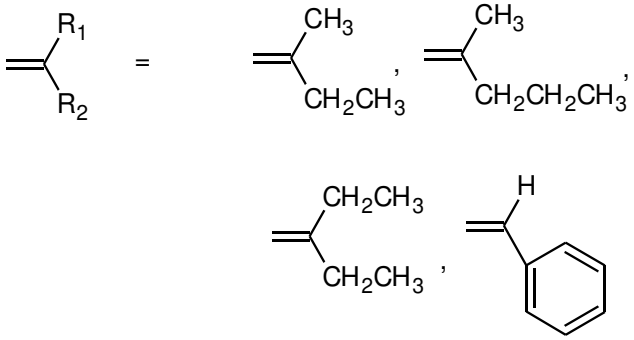
8. Veerachamy Alagarsamy et al., synthesized 1,4-Disubstituted 1,2,4-triazolo[4,3-a] Quinazolin-5(4H)ones.[15]



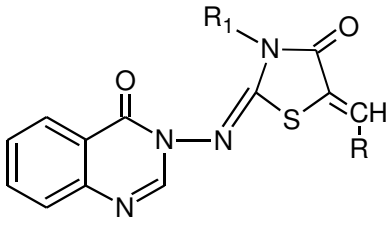
R= -H, -CH_3, -C_2H_5, -$(CH_2)_2CH_3$, -CH_2Cl

9. Veerachamy Alagarsamy et al., synthesized 3 –(4-methoxy phenyl) 2-substituted amino Quinazolin-4(3H)ones as analgesic & anti-inflammatory agents.[16]

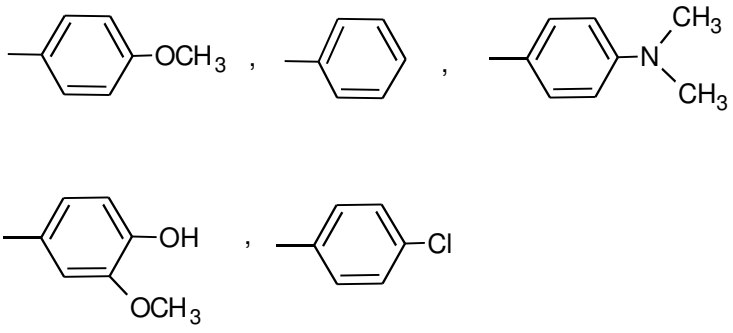




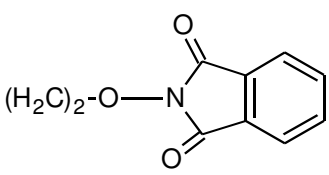
10. Usha Ameta et al., synthesized 3-[(5-arylidene-4-oxo-1,3-thiazolidin-2-yliden)amino]-2-phenyl quinazolin-4(3H) ones and their ethoxy phthalimide derivatives.[17]



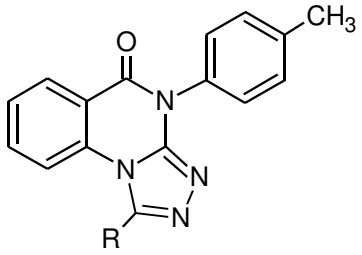
R=



R_1=

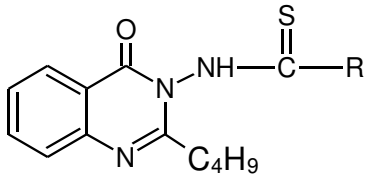


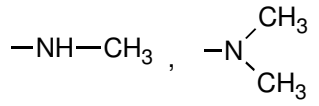
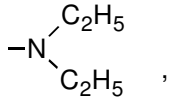
11. Veerachamy Alagarsamy et al., synthesized 1-substituted 4- (3-methyl phenyl) 1,2,4-triazolo[4,3-a] Quinazolin-5(4H)ones.[18]

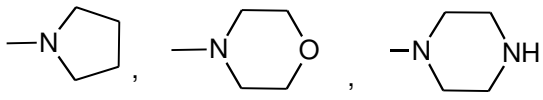


R= -H, -CH_3, -C_2H_5, -$(CH_2)_2CH_3$, -CH_2Cl

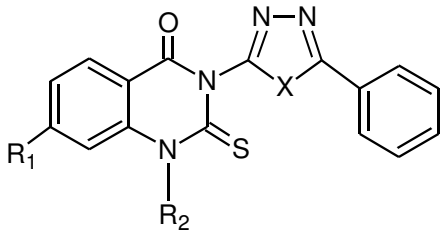
12. Veerachamy Alagarsamy et al., synthesized novel -2 –butyl 3-substituted Quinazolin-4(3H)ones.[19]



R=  , ,  ,



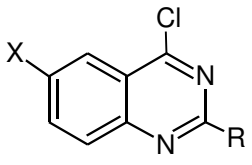
13. Vinod K.Tiwari et al., synthesized 3-heteroaryl-2-thioxo-2,3-dihydro quinazolin-4-(1H)-one.[20]



X= O,S R= H,Cl

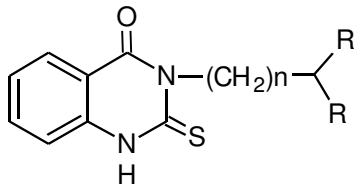
R_1= H,CH_3 R_2= CH_3,H

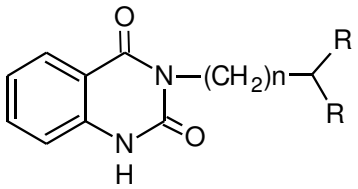
14. P.Mani Chandrika et al., Synthesized novel 2,4,6-tri substituted quinazoline derivatives as anti bacterial and cytotoxic agents.[21]



X= H R= C_6H_5, CH_3, CF_3, I, Br

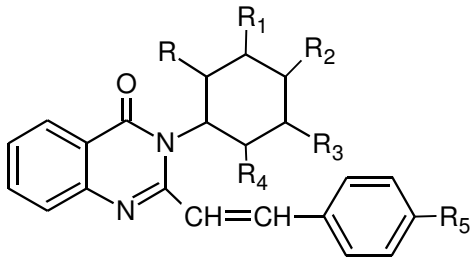
15. M.B. Raju et al., Synthesized 3- [(N,N-Dialkyl amino)alkyl)-1,2,3,4-tetrohydro – (1H)-thio quinazolin-4(3H)-ones and their oxo analogues as antihistaminic agents.[22]





R= $-CH_3$, $-CH_2CH_3$, C_4H_9 n= 2, 3

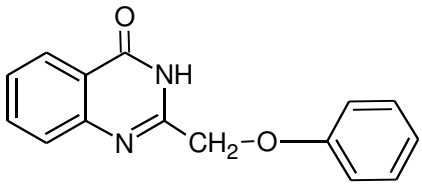
16. E.M. Jessy et al., Synthesized some novel Quinazolones.[23]



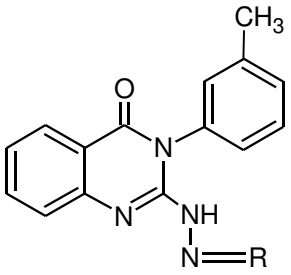
R= COOH, H R_1= H, COOH R_2=H, Br

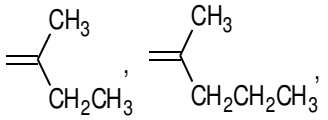
R_3= Cl, H R_4= H, Cl R_5= NO_2, OCH_3, F, OH

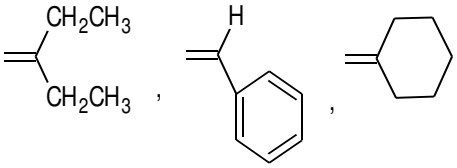
17. L. Cipak et al., Synthesized 2-phenoxy methyl 3-H Quinazolin-4-one as anticancer agents.[24]



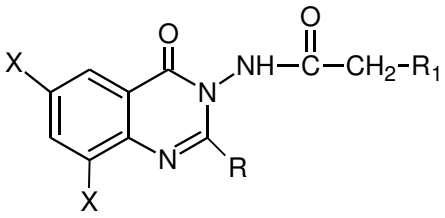
18. Maykel cruz-Monteagudo et al., Synthesized 3-(3-Methyl phenyl)-2-substituted amino-3H- Quinazolin-4-ones as analgesic, anti-inflammatory & ulcerogenic agents.[25]



R = 



19. N.M.Raghavendra et al., Synthesized Novel substituted piperazinyl quinazolin-3-(4H)-ones as antimicrobial agents.[26]



X= H, Br

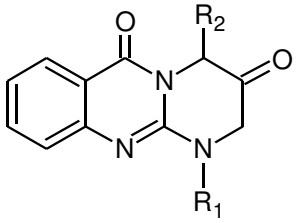
R= C_6H_5, CH_3

R1= piperazinyl, 4-methyl piperazin-1-yl,

4-ethyl piperazin-1-yl,

4-phenyl piperazin-1-yl

20. Chang Xie et al., Synthesized imidazo [2, 1-b] quinazoline-2,5 (1H,3H)-diones.[27]

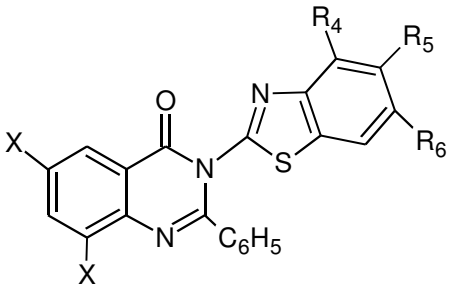


R_1= Ph, 4-chloro phenyl,

3-methyl phenyl

R_2= H, CH_3, $C_6H_5CH_2$

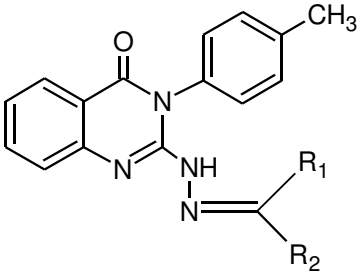
21. Sachin S. Laddha et al., Synthesized 6,8 disubstituted 2-phenyl 3[substituted-benzothiazol-2-yl]-4(3H)-quinazolinones.[28]

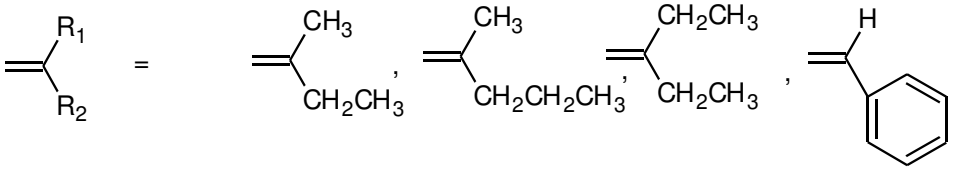


X= Br, R_4= H, OCH_3, CH_3, OC_2H_5 R_5= H, OCH_3, CH_3, OC_2H_5

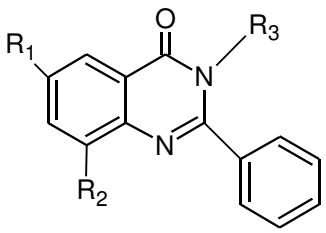
R_6= H, OCH_3, NO_2, OC_2H_5

22. Veerachamy Alagarsamy et al., synthesized 3 –(4-methyl phenyl) 2-substituted amino Quinazolin-4(3H)ones as analgesic & anti-inflammatory agents.[29]

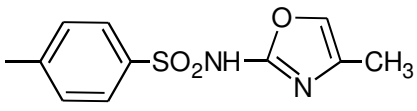
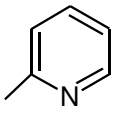




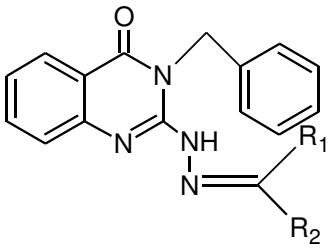
23. Periyasamy Selvam et al., Synthesized novel 2-phenyl 3-Disubstituted quinazolin-4(3H)-ones.[30]

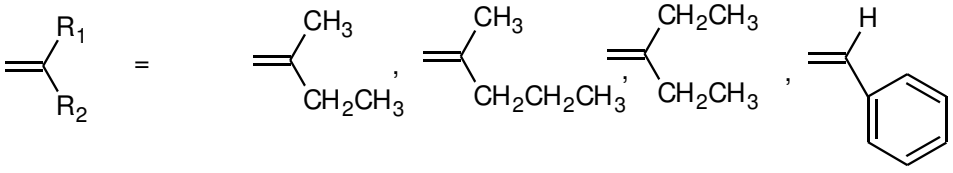


R_1= H, Br R_2= H, Br

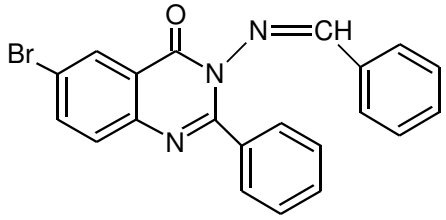
R_3=  , 

24. Veerachamy Alagarsamy et al., synthesized 3 –(benzyl) 2-substituted amino Quinazolin-4(3H)ones as analgesic & anti-inflammatory agents.[31]

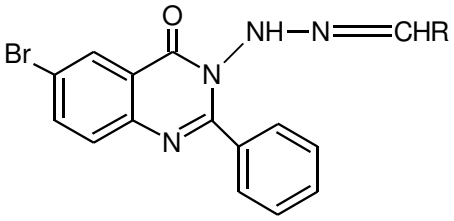




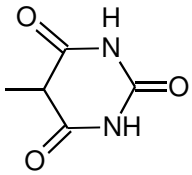
25. N.M.Raghavendra, M.S.Niranjan et al., reported on the synthesis of substituted 2-phenyl quinazolin-4-ones and studied their antitumor and antimicrobial activity.[32]



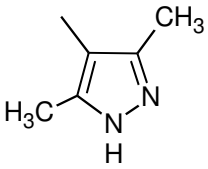
26. Mohamed A Abdo et al., reported on some reactions of 2-phenyl-4-(3H) quinazolinones.[33]



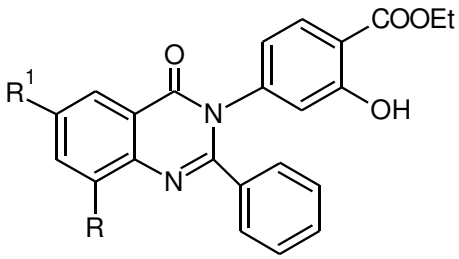
R= COOEt ,



,

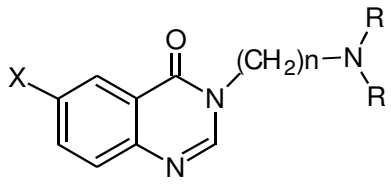


27. Anil.K.Sengupta, Tapas Bhattacharya reported on synthesis and antimicrobial activity of some substituted 2-phenyl -3-aryl quinazol-4-ones.[34]



I) R=R[1]=H, II) R=H, R[1]=Br, III) R=R[1]=Br

28. S.Dev Singh et al., reported on synthesis and H_1-antihistaminic evaluation of 3-[(N,N-dialkyl amino) alkyl]-6-halo-2-phenyl-3,4-dihydro quinazolin-4(3H)-ones.[35]

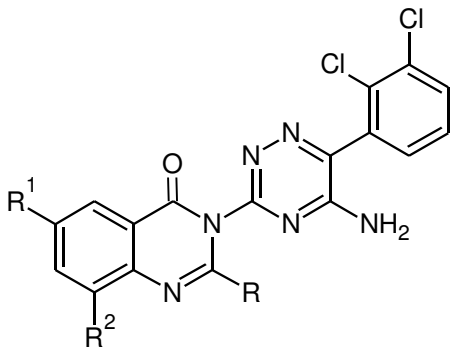


X= Br, I

n= 2, 3

R= CH_3, C_2H_5, C_4H_9

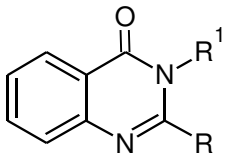
29. P.Selvam et al., reported on synthesis and cytostatic activity of some 3-[5-amino-6(2,3 dichlorophenyl) – [1,2,4] triazin-3yl]- 6,8 dibromo-2-substituted -3H-Quinazolin-4-ones. [36]



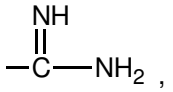
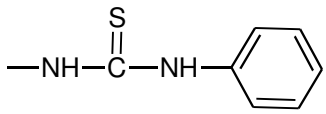
R= CH_3, C_2H_5, C_6H_5

R^1, R^2= H, Br

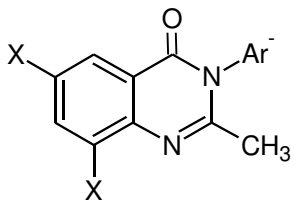
30. R.K. Kawadkar, B.J. Ghiya reported on synthesis of New Quinazolin-4-one compounds of Medicinal importance.[37]



R= CH_3, C_6H_5

R^1=H,  , 

31. Pradeep Mishra, P. Paneer Selvam reported on the synthesis of 2- methyl Quinazolin-$(3H) ones and studied their antimicrobial activity.[38]

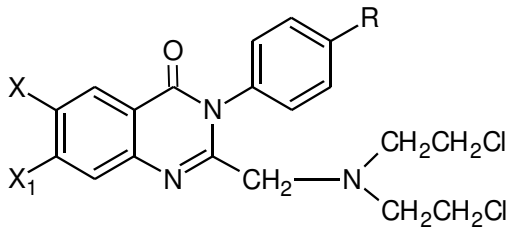


X= H, Br

Ar= o-C_6H_4COOH, o-C_6H_4OH,

p- $C_6H_4NO_2$, p-$C_6H_4SO_3H$

32. V. Malla Reddy, V. Murugan et al., reported on the synthesis of some 2-alkyl 3-aryl-4 (3H) Quinazolinones as possible antitumor agents.[39]

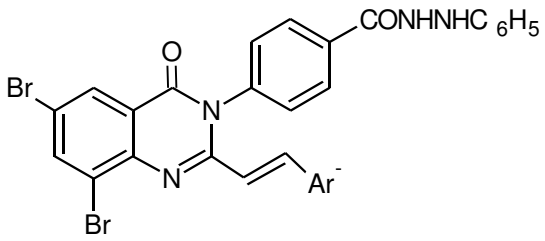


R= 4-Cl, 4-OC_2H_5, 4-NO_2

X= H, 6-Cl

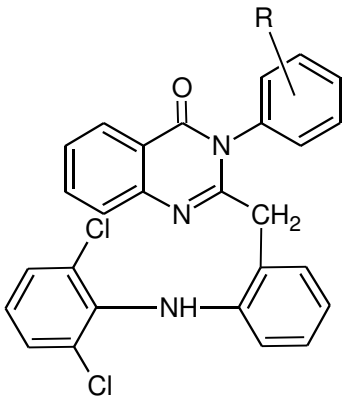
X_1= 6-Br, 8-Cl

33. V. Murugan, et al.,reported on the synthesis of 2- substituted Quinazolin-4 (3H)-ones as a new class of anticancer agents.[40]



Ar= -C_6H_5, -CH=CH-C_6H_5, -m-$C_6H_5NO_2$

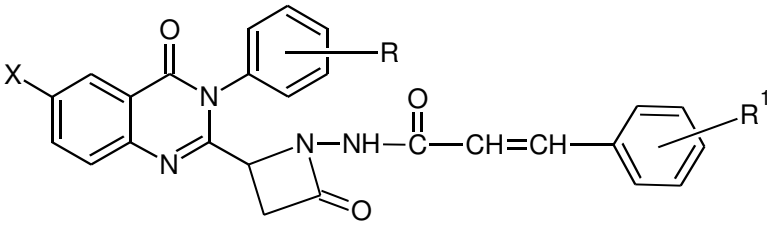
34. N.B.Patel and J.D. lilakar reported on the synthesis and antibacterial activity of new substituted 4(3H) Quinazolinones.[41]



R=H, 2-NO_2, 2-CH_3, 2-OCH_3, 2-Cl,

3-NO_2, 3-CH_3, 3-OCH_3, 3-Cl,

35. Ashok Kumar, V.K. Srivastava reported on the synthesis and anti-inflammatory activity of some New 2, 3 disubstituted-6-monosubstituted-Quinazolin-4(3H)-ones.[42]

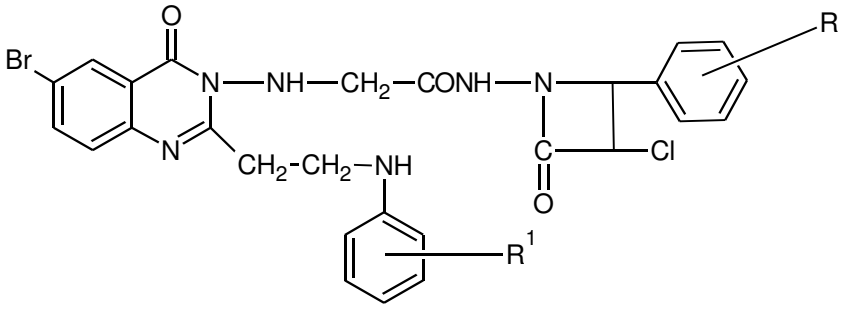


X= Br, H

R= o-Cl, o-OCH_3, m-Cl, H

R^1=m-OCH_3, p-OH, p-$N(CH_3)_2$, p-OCH_3

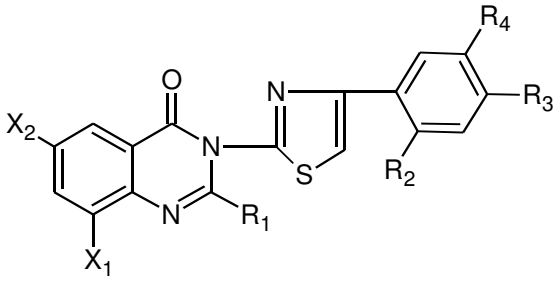
36. Ashok Kumar, Mirdula Tyagi et al.,reported on the synthesis and hypotensive activity of New potential Quinazolinones.[43]



R= 4-OCH_3, 3-OCH_3, 4-OH, 4-$N(CH_3)_2$, H

R^1= o-Cl, H, p-Cl,p-OCH_3

37. P.C. Sarkar et al.,on the synthesis and biological evaluation of some New 2-aryl/ substituted aryl -6,8-substituted Quinazol-4(3H)-ones.[44]

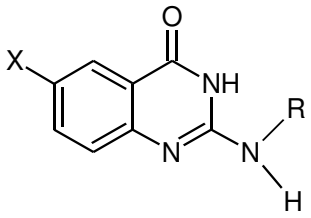


X1=X2=R2=R3=R4=H R1= C6H5-

X1=X2=R2=R3=R4=H R1= p-ClC6H4-

X1=X2=R2=R3=R4=H R1= m-ClC6H4-

38. Bernard Pirotte et al.,reported on the synthesis and K_{ATP} channel activity of 2-alkyl amino-6-halogeno Quinazolin-4(3H)-ones.[45]



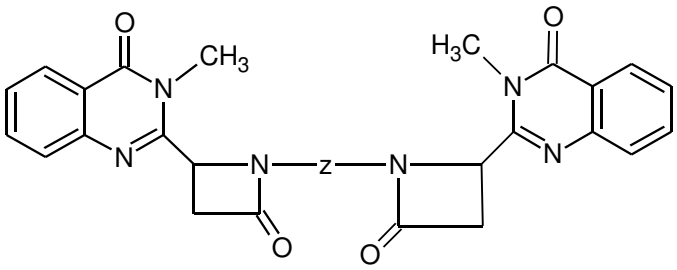
(i) X= Cl, I $R=CH(CH_3)_2$

(ii) X= Cl, I $R=CH(CH_3)CH_2CH_3$

(iii) X= Cl, I $R=CH(CH_3)CH(CH_3)_2$

(iv) X= Cl, I $R=CH_2C_6H_{11}$

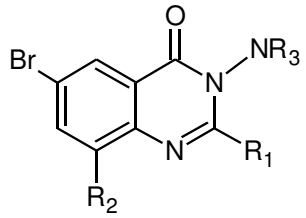
39. PSN Reddy et al., reported on the synthesis of novel Bis Quinazolinyl-Beta lactams.[46]



Z=1, 4 C_6H_4, 4,4'- C_6H_4- C_6H_4,

4,4'- C_6H_3 (3-CH_3)- C_6H_3(3'-CH_3)

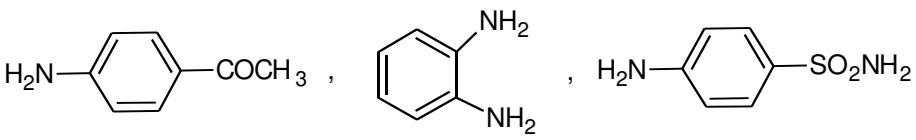
40. H.M.F, Madkour reported on the reactivity of 4H-3, 1-benzoxazin-4-ones towards nitrogen and carbon nucleophilic reagents.[47]



R_1= Isopropyl, Methyl

R_2= Br

R_3= Nitrogen nucleophiles – NH_2OH, HCl,

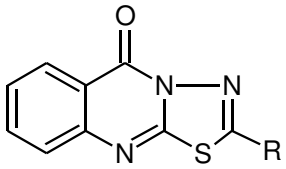


Carbon electrophiles: Benzaldehyde,

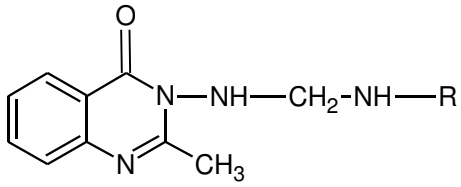
4-methoxy benzaldehyde,

4-chloro benzaldehyde

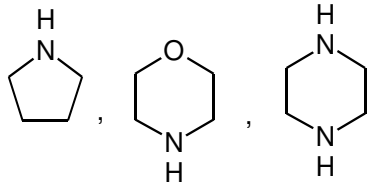
41. V.Alagarsamy et al., Synthesized 2 substituted (1,3,4) Thiadiazolo Quinazolines.[48]



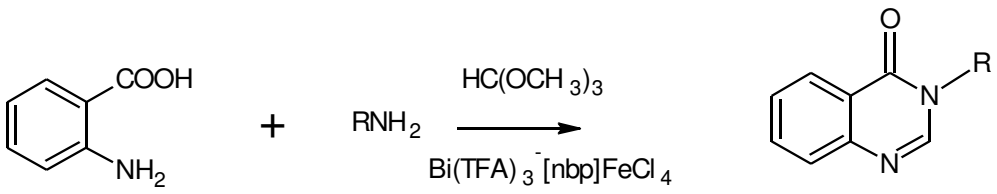
42. V.Alagarsamy et al., Synthesized Novel-2-Methyl 3-Substituted Methylamino – (3H)- Quinazolin-4-ones as Anti HIV, Antibacterial & Antifungal agents.[49]



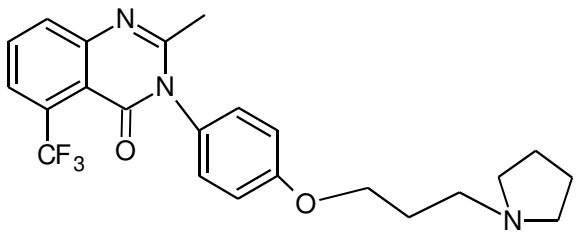
R= $(CH_3)_2$, $(C_2H_5)_2$,



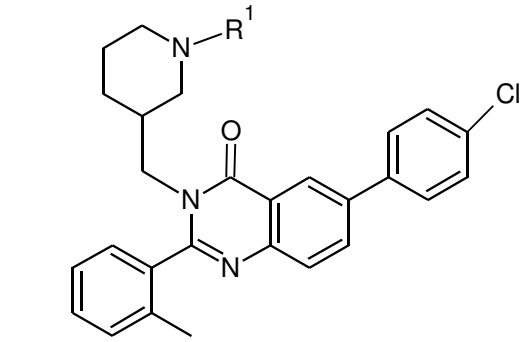
43. Ahmad R. Khosropour, Iraj Mohammadpoor-Baltorka and Hamid Ghorbankhani, Bi(TFA)3–[nbp]FeCl4: a new, efficient and reusable promoter system for the synthesis of 4(3H)-quinazolinone derivatives.[50]

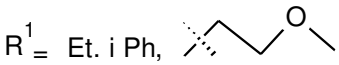


44. Tsuyoshi Nagase, Takashi Mizutani et al., Synthesis and Evaluation of Structurally Constrained Quinazolinone Derivatives as Potent and Selective Histamine H3 Receptor Inverse Agonists.[51]

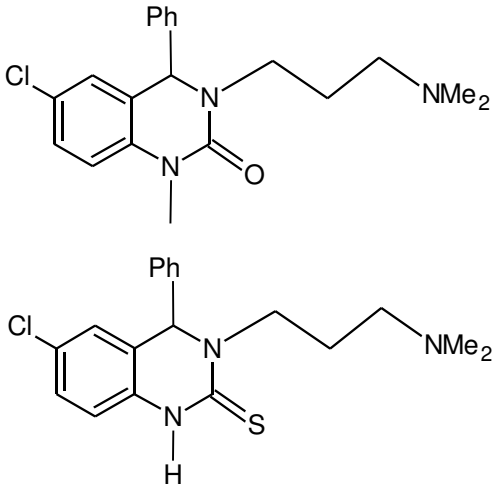


45. Joachim Rudolph, William P. Esler et al., Synthesis a Quinazolinone Derivatives as Orally Available Ghrelin Receptor Antagonists for the Treatment of Diabetes and Obesity.[52]

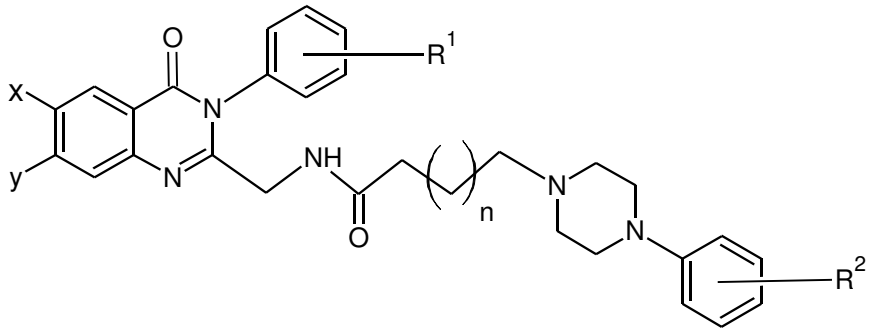




46. Hirohiko Hasegawa, Masami Muraoka et al., Discovery of a Novel Potent Na+/Ca2+ Exchanger Inhibitor: Design, Synthesis and Structure–Activity Relationships of 3,4-Dihydro-2(1H)-quinazolinone Derivatives.[53]



47. Yong Ho Na, Sung Ho Hong et al., Synthesis of Novel quinazolinone derivatives as 5-HT7 receptor ligands.[54]



X = H, H, H, H, H

Y= H, H, H, H, H

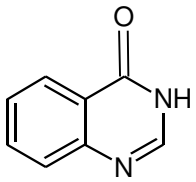
R1= H, H, H, H, H

R2=H, o-Cl, p-Cl, p-Me, 2,3-Me_2

n= 0, 0, 0, 0, 0

OBJECTIVE OF PRESENT WORK

Quinazolin-4-(3H)-one is a versatile lead molecule for the design of potential bioactive agents.[30, 55]



quinazolin-4(3*H*)-one

From the literature review, it was known that most of the Quinazolin-4-(3H)- ones having substitution at C-2 and N-3 positions possess various interesting pharmacological activities.

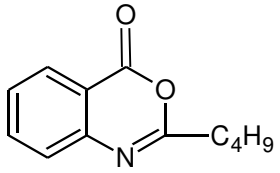
In the present work, Novel 2-butyl-3-amino (substituted)quinazolin-4(3H)-ones were synthesized and their analgesic and anticonvulsant activities were evaluated.

The objective of the present work can be summarized as follows:

I) Synthesis:

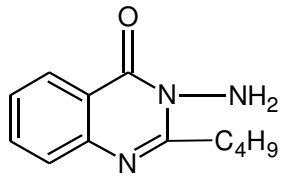
To synthesize 2-butyl-3-substituted amino quinazolin-4(3H)-one derivatives by the following steps

- First step is the cyclization of Anthranilic acid with Valeric anhydride to give 2-butyl-4H-3, 1-benzoxazin-4-one.



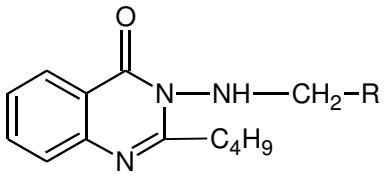
2-butyl-4*H*-3,1-benzoxazin-4-one

- Second step is the condensation of 2-butyl-4H-3,1-benzoxazin-4-one with hydrazine hydrate to yield 3-amino-2n-butyl Quinazolin-4(3H)-one



3-amino-2-butylquinazolin-4(3*H*)-one

- Third step is the substitution of various amines to yield 3-substituted amino-2n-butyl Quinazolin-4(3H)-one derivatives [56, 57]



3-substituted amino-2n-butyl Quinazolin-4(3H)-one

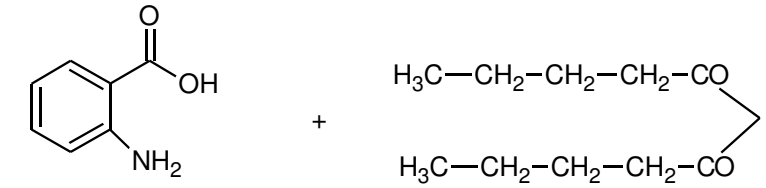
II) Characterization:

Characterization of the synthesized compounds by the analytical technique like **thin layer chromatography, Infrared spectral analysis, Nuclear magneticresonance spectral analysis** methods.

III) Pharmacological Screening:

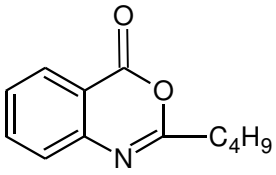
- ✓ Screening of the synthesized compounds for **Anticonvulsant activity** against electrically induced seizures.
- ✓ Screening of the synthesized compounds for **Analgesic activity** by aceticacid induced writhing method.

SCHEME OF REACTION



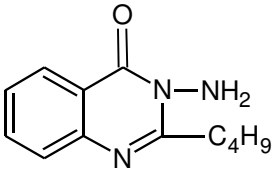
Anthranilic Acid + Valeric anhydride

Reflux for 3 hours

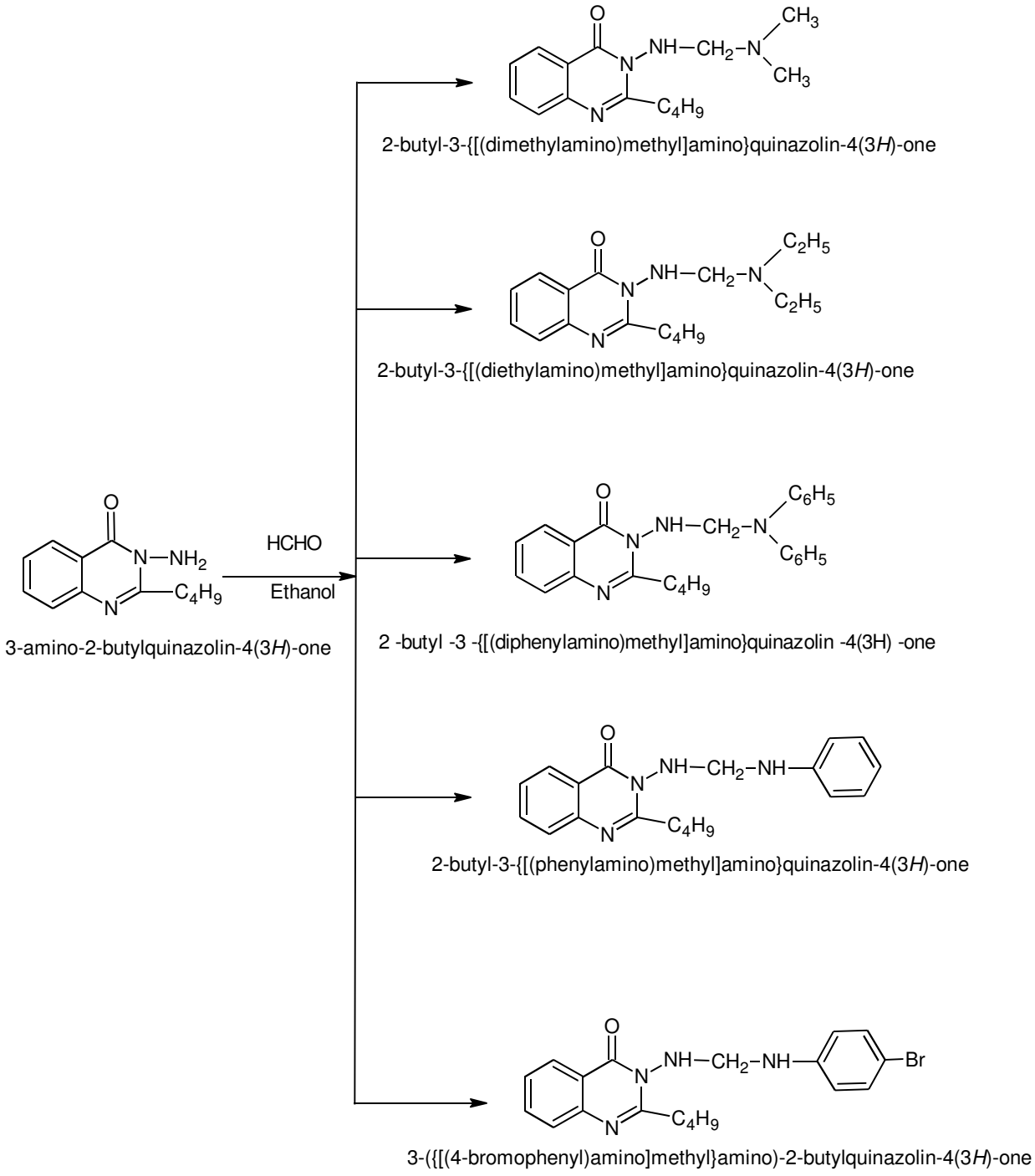


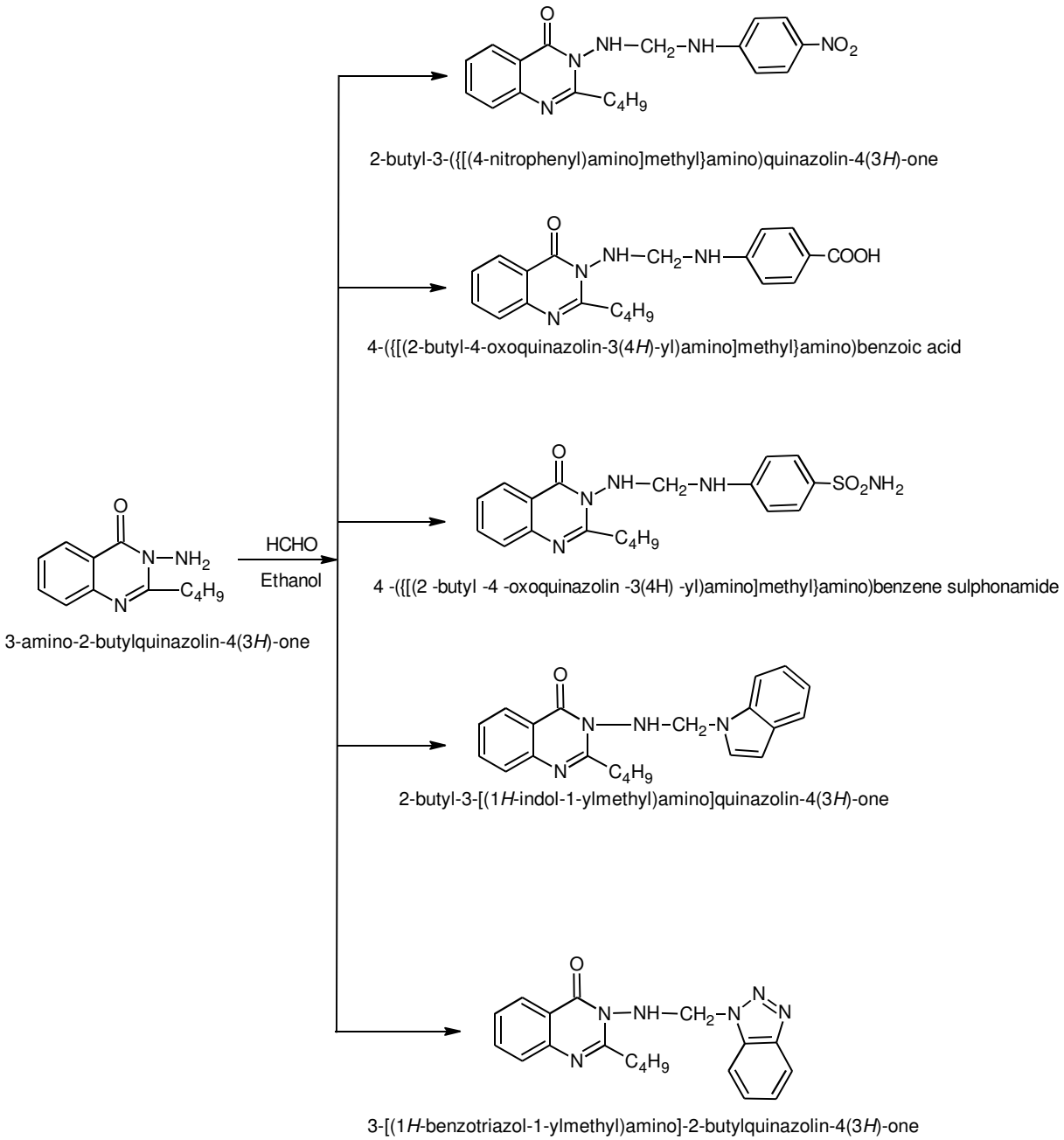
2-butyl-4*H*-3,1-benzoxazin-4-one

Ethanol, $H_2N—NH_2.H_2O$



3-amino-2-butylquinazolin-4(3*H*)-one


HCHO
Ethanol
2-butyl-3-{[(dimethylamino)methyl]amino}quinazolin-4(3H)-one
2-butyl-3-{[(diethylamino)methyl]amino}quinazolin-4(3H)-one
3-amino-2-butylquinazolin-4(3H)-one
2 -butyl -3 -{[(diphenylamino)methyl]amino}quinazolin -4(3H) -one
2-butyl-3-{[(phenylamino)methyl]amino}quinazolin-4(3H)-one
3-({[(4-bromophenyl)amino]methyl}amino)-2-butylquinazolin-4(3H)-one


O
NH—CH2—NH
NO2
N
C4H9
2-butyl-3-({[(4-nitrophenyl)amino]methyl}amino)quinazolin-4(3H)-one
COOH
4-({[(2-butyl-4-oxoquinazolin-3(4H)-yl)amino]methyl}amino)benzoic acid
SO2NH2
4 -({[(2 -butyl -4 -oxoquinazolin -3(4H) -yl)amino]methyl}amino)benzene sulphonamide
NH—CH2-N
2-butyl-3-[(1H-indol-1-ylmethyl)amino]quinazolin-4(3H)-one
N—NH—CH2-N
N
3-[(1H-benzotriazol-1-ylmethyl)amino]-2-butylquinazolin-4(3H)-one
HCHO
Ethanol
N—NH2
3-amino-2-butylquinazolin-4(3H)-one

SYNTHESIS

EXPERIMENTAL WORK

SYNTHESIS

STEP I:

SYNTHESIS OF 2(N-BUTYL) -3H-QUINAZOLIN-4-ONE[19]

CHEMICALS REQUIRED

Anthranilic acid

Pentanoic anhydride

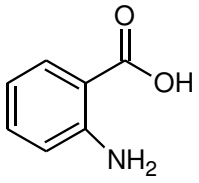
PROCEDURE

A mixture of anthranilic acid (0.01 mol) and pentanoic anhydride (0.05 mol) was refluxed under anhydrous conditions for 3 hours.

Excess liquid was distilled off under reduced pressure and the reaction mixture was cooled to room temperature.

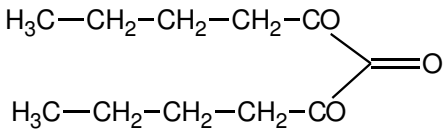
SYNTHESIS OF 2-BUTYL-4H-3,1-BENZOXAZIN-4-ONE:

STEP - I:

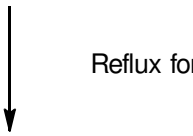


Anthranilic Acid

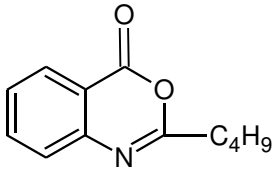
+



Valeric anhydride



Reflux for 3 hours



2-butyl-4*H*-3,1-benzoxazin-4-one

SYNTHESIS

STEP II:

SYNTHESIS OF 3-AMINO-2-(N-BUTYL)-3H-QUINAZOLINE-4-ONE[19]

CHEMICALS REQUIRED

Pyridine

Hydrazine Hydrate

Conc. Hydrochloric Acid

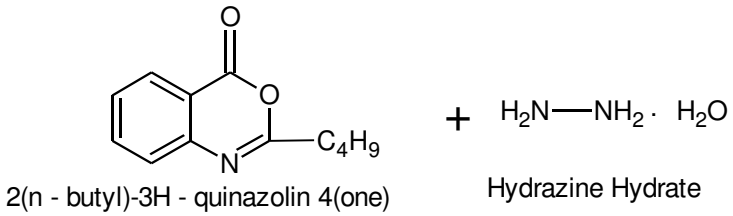
PROCEDURE

The solid obtained was dissolved in pyridine (50ml) and hydrazine hydrate(0.02 mol) was added to it and then refluxed for 4 hours. Cool to room temperature and pour it in to a mixture of ice (50g) and conc. Hydrochloric acid (50 ml).

The reaction mixture was kept overnight. The solid separated was filtered, Washed well with water, dried and recrystallised from ethanol.

SYNTHESIS OF 3-AMINO-2-BUTYLQUINAZOLIN-4(3H)-ONE:

STEP - II:



3-amino-2-butylquinazolin-4(3*H*)-one

SYNTHESIS [56, 57, 58]

STEPIII

SYNTHESIS OF 3-SUBSTITUTED-2-(N-BUTYL)-3H-QUINAZOLINE-4-ONE[49]

CHEMICALS REQUIRED

Amine

Formaldehyde(37-41%)

Dimethyl formamide

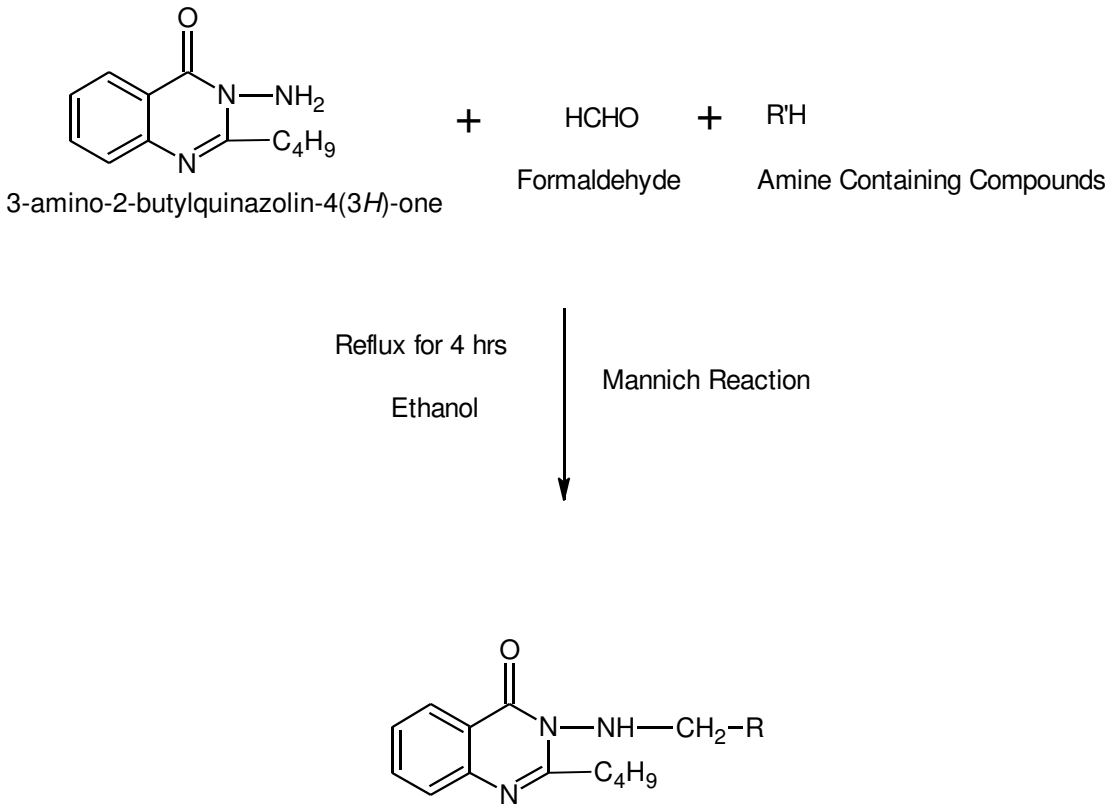
Ethanol

PROCEDURE

A mixture of formalin (37-41% ; 1ml) and amine (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min . After cooling , it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol .

SYNTHESIS OF 2-BUTYL-3-{[(AMINO SUBSTITUTED)METHYL]AMINO} QUINAZOLIN-4(3H)-ONE:

Step III :



2-butyl-3-{[(amino substituted) methyl]amino}quinazolin-4(3H)-one

SYNTHESIS

stepIII

Synthesis of 2-(n-butyl)-3-{[(dimethylamino)methyl]amino}quinazoline -4(3H)-one[49]

CHEMICALS REQUIRED

Dimethyl Amine

Formaldehyde(37-41%)

Dimethyl formamide

Ethanol

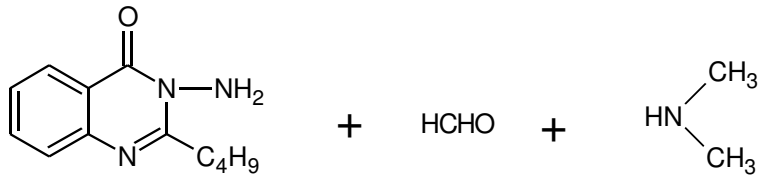
PROCEDURE

A mixture of formalin (37-41% ; 1ml) and dimethyl amine (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one (0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min. After cooling, it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol.

SYNTHESIS OF 2-BUTYL-3-{[(DIMETHYLAMINO)METHYL]AMINO} QUINAZOLINE-4(3H)-ONE:

STEP III:

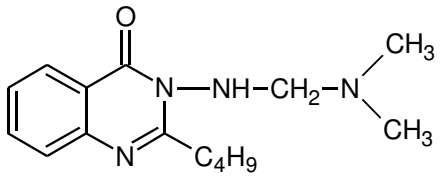
Substitution with Dimethylamine :



3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde Dimethyl amine

Reflux for 4 hrs
Ethanol

Mannich Reaction



2-butyl-3-{[(dimethylamino)methyl]amino}quinazolin-4(3*H*)-one

SYNTHESIS

stepIII

Synthesis of 2-(n-butyl)-3-{[(diethylamino)methyl]amino}quinazoline -4(3H)-one[49]

CHEMICALS REQUIRED

Diethyl Amine

Formaldehyde(37-41%)

Dimethyl formamide

Ethanol

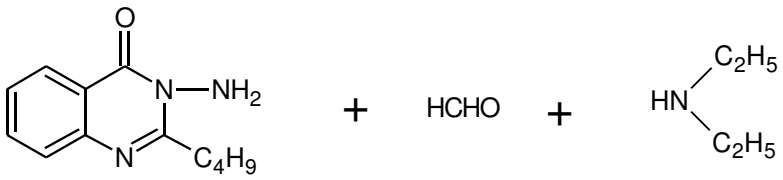
PROCEDURE

A mixture of formalin (37-41%; 1ml) and diethyl amine (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H) quinazolin-4-one (0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min. After cooling, it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol.

SYNTHESIS OF 2-BUTYL-3-{[(DIETHYLAMINO)METHYL]AMINO} QUINAZOLIN-4(3H)-ONE:

STEP III:

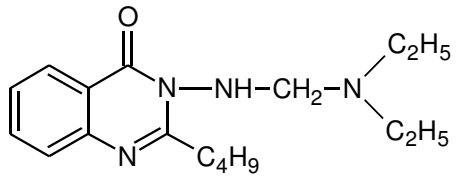
Substitution with Diethylamine :



3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde Diethyl amine

Reflux for 4 hrs
Ethanol

Mannich Reaction



2-butyl-3-{[(diethylamino)methyl]amino}quinazolin-4(3*H*)-one

SYNTHESIS

stepIII

Synthesis of 2-(n-butyl)-3-{[(diphenylamino)methyl]amino}quinazoline -4(3H)-one[49]

CHEMICALS REQUIRED

Diphenyl Amine

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

PROCEDURE

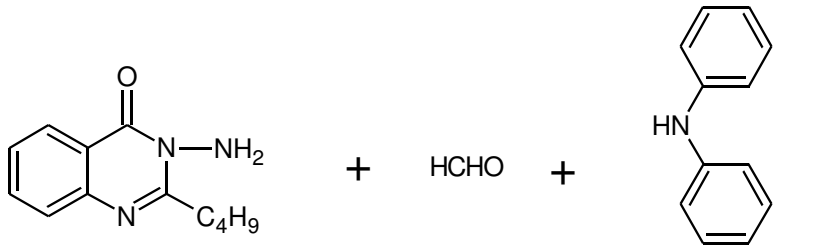
A mixture of formalin (37-41%; 1ml) and diphenylamine (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min . After cooling , it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol .

SYNTHESIS OF 2-BUTYL-3-{[(DIPHENYLAMINO)METHY]}

QUINAZOLIN-4(3H)-ONE:

STEP III:

Substitution with Diphenylamine :

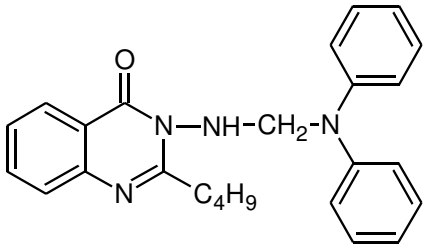


3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde Diphenyl amine

Reflux for 4 hrs

Ethanol

Mannich Reaction



2-butyl-3-{[(diphenylamino)methyl]amino}quinazolin-4(3H)-one

SYNTHESIS

stepIII

Synthesis of 2-(n-butyl)-3-{[(phenylamino)methyl]amino}quinazoline -4(3H)-one[49]

CHEMICALS REQUIRED

Aniline

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

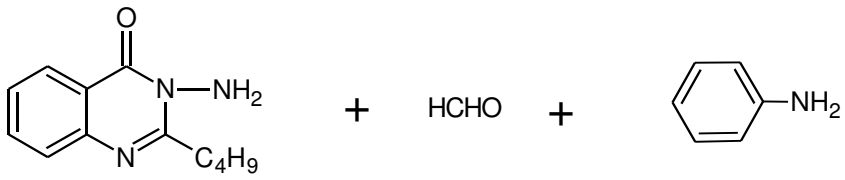
PROCEDURE

A mixture of formalin (37-41%; 1ml) and aniline (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)-quinazolin-4-one (0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min. After cooling, it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol.

SYNTHESIS OF 2-BUTYL-3-{[(PHENYLAMINO)METHYL]AMINO} QUINAZOLIN-4(3H)-ONE:

STEP III:

Substitution with Aniline :

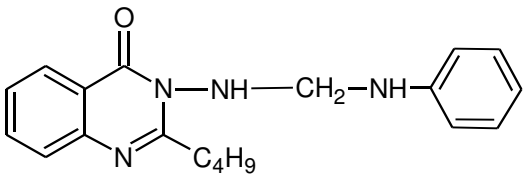


3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde aniline

Reflux for 4 hrs

Ethanol

Mannich Reaction



2-butyl-3-{[(phenylamino)methyl]amino}quinazolin-4(3*H*)-one

SYNTHESIS

stepIII

Synthesis of 3-({[(4-bromophenyl)amino]methyl}amino) -2-butylquinazolin--4(3H)one[49]

CHEMICALS REQUIRED

4- bromo Aniline

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

PROCEDURE

A mixture of formalin (37-41% ; 1ml) and 4- bromoaniline (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min . After cooling , it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol .

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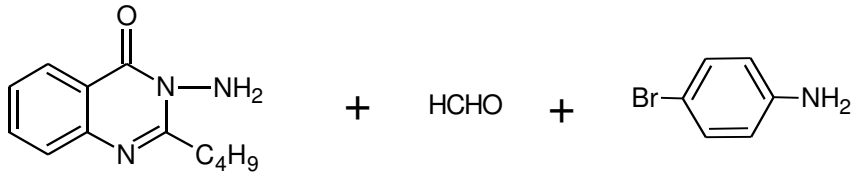
SYNTHESIS OF 3-({[(4-BROMOPHENYL)AMINO]METHYL}AMINO) -2-BUTYLQUINAZOLIN-4(3H)-ONE:

STEP III:

Substitution with 4 - Bromo Aniline :

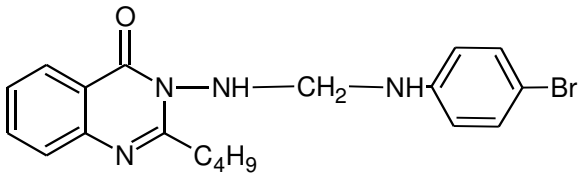


3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde 4-bromoaniline

Reflux for 4 hrs

Ethanol

Mannich Reaction



3-({[(4-bromophenyl)amino]methyl}amino)-2-butylquinazolin-4(3*H*)-one

SYNTHESIS

stepIII

Synthesis of 2-butyl 3-({[(4-nitrophenyl)amino]methyl}amino) quinazolin -4(3H)-one[49]

CHEMICALS REQUIRED

4- Nitro Aniline

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

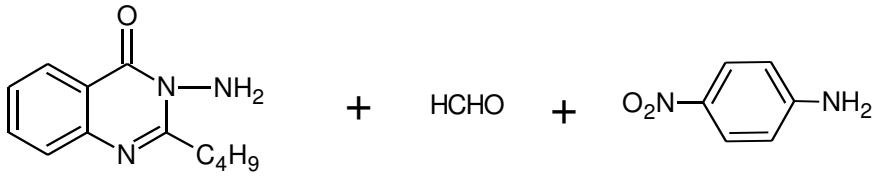
PROCEDURE

A mixture of formalin (37-41% ; 1ml) and 4-nitro aniline (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min . After cooling , it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol .

SYNTHESIS OF 2-BUTYL-3-({[(4-NITROPHENYL)AMINO]METHYL} AMINO)QUINAZOLIN-4(3H)-ONE:

STEP III:

Substitution with 4 - Nitro Aniline :

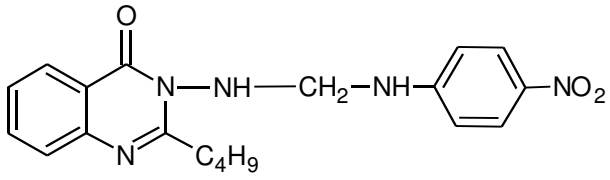


3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde 4-nitroaniline

Reflux for 4 hrs

Ethanol

Mannich Reaction



2-butyl-3-({[(4-nitrophenyl)amino]methyl}amino)quinazolin-4(3*H*)-one

SYNTHESIS

stepIII

Synthesis of 4-({[(2-butyl-4-oxoquinazolin-3(4H) -yl) amino] methyl} amino) benzoic acid[49]

CHEMICALS REQUIRED

Para amino benzoic acid

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

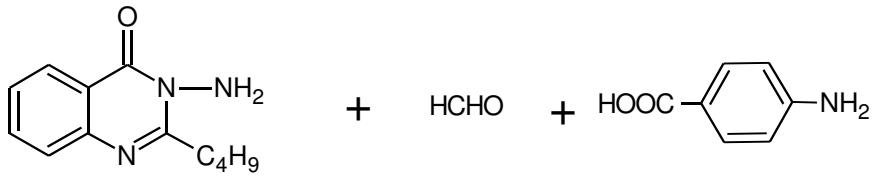
PROCEDURE

A mixture of formalin (37-41% ; 1ml) and para amino benzoic acid (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min. After cooling, it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol.

SYNTHESIS OF 4-({[(2-BUTYL-4-OXOQUINAZOLIN-3(4H)-YL)AMINO] METHYL}AMINO)BENZOIC ACID:

STEP III:

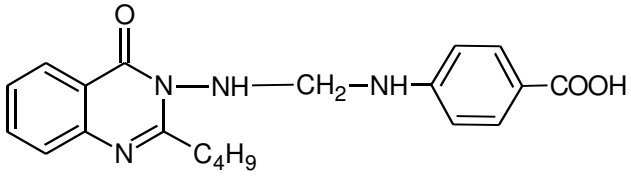
Substitution with Para Amino BenzoicAcid :



3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde Para Amino BenzoicAcid

Reflux for 4 hrs
Ethanol

Mannich Reaction



4-({[(2-butyl-4-oxoquinazolin-3(4*H*)-yl)amino]methyl}amino)benzoic acid

SYNTHESIS

stepIII

Synthesis of 4-({[(2-butyl-4-oxoquinazolin-3(4H)- yl) amino]methyl} amino) benzene sulphonamide[49]

CHEMICALS REQUIRED

Sulphanilamide

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

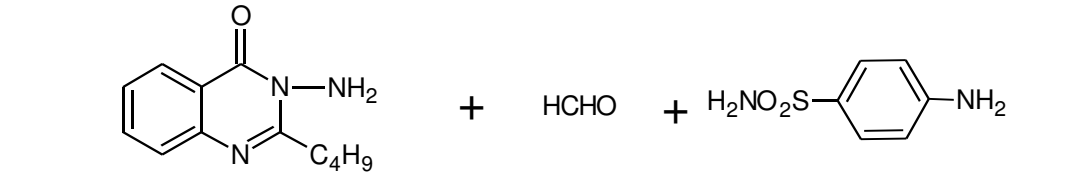
PROCEDURE

A mixture of formalin (37-41% ; 1ml) and sulphanilamide(0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min . After cooling , it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol .

SYNTHESIS OF 4-({[(2-BUTYL-4-OXOQUINAZOLIN-3(4H)- YL) AMINO] METHYL} AMINO)BENZENE SULPHONAMIDE:

STEP III:

Substitution with Sulphanilamide :

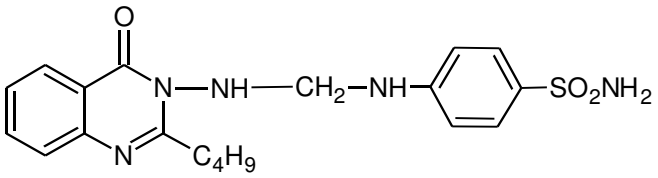


3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde 4-aminobenzenesulfonamide

Reflux for 4 hrs

Ethanol

Mannich Reaction



4-({[(2-butyl-4-oxoquinazolin-3(4H)- yl) amino]methyl} amino)

benzene sulphonamide

SYNTHESIS

stepIII

Synthesis of 2-butyl-3-[(1H-indol-1-yl methyl)amino] quinazolin-4(3H) –one[49]

CHEMICALS REQUIRED

Indole

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

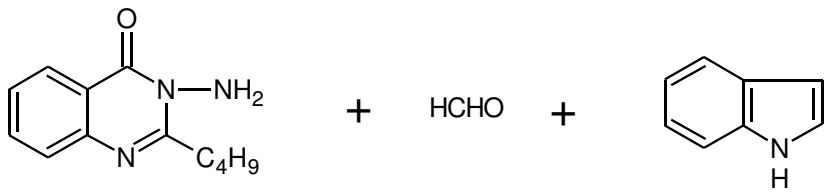
PROCEDURE

A mixture of formalin (37-41% ; 1ml) and indole (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min. After cooling, it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol.

SYNTHESIS OF 2-BUTYL-3-[(1H-INDOLE-1YLMETHYL)AMINO] QUINAZOLIN-4(3H)-ONE:

STEP III:

Substitution with Indole :

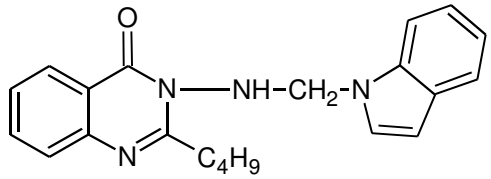


3-amino-2-butylquinazolin-4(3*H*)-one Formaldehyde Indole

Reflux for 4 hrs

Ethanol

Mannich Reaction



2-butyl-3-[(1*H*-indol-1-ylmethyl)amino]quinazolin-4(3*H*)-one

SYNTHESIS

stepIII

Synthesis of 3-[(1H-benztriazole-1yl methyl)amino]-2-butyl quinazolin-4(3H)-one[49]

CHEMICALS REQUIRED

Benztriazole

Formaldehyde (37-41%)

Dimethyl formamide

Ethanol

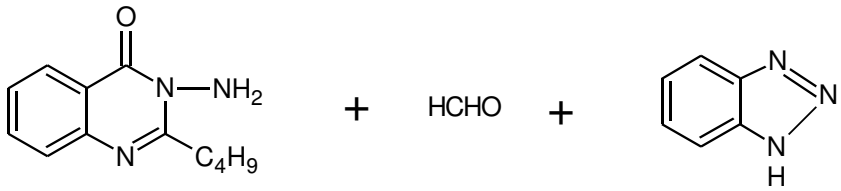
PROCEDURE

A mixture of formalin (37-41%; 1ml) and benztriazole (0.005mol) drop by drop with stirring to a slurry of 3-amino-2-butyl-3(H)quinazolin-4-one(0.005 mol) in dimethylformamide (15 ml). The reaction mixture was heated on a water bath for about 25min. After cooling, it was poured in to ice water. The solid obtained was filtered washed with water, dried and recrystallized from ethanol.

SYNTHESIS OF 3-[(1H-BENZOTRIAZOL-1YLMETHYL)AMINO]-2-BUTYL QUINAZOLIN-4(3H)-ONE:

STEP III:

Substitution with Benztriazole :

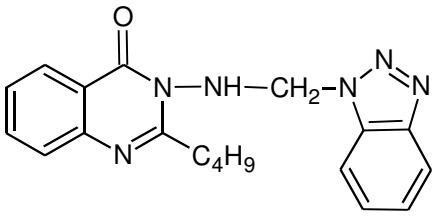


3-amino-2-butylquinazolin-4(3*H*)-one + Formaldehyde + Benztriazole

Reflux for 4 hrs

Ethanol

Mannich Reaction



3-[(1*H*-benzotriazol-1-ylmethyl)amino]-2-butylquinazolin-4(3*H*)-one

PHYSICAL DATA OF THE TITLED COMPOUNDS

Table No :1

58

Compound Code	Chemical Name	Molecular Formula	Molecular Weight(grams)	Percentage Yield	Appearance
A1	2-butyl-3-{[(dimethylamino)methyl] amino} quinazolin-4(3*H*)-one	$C_{15}H_{22}N_4O$	274.361	91.05%	Solid
A2	2-butyl-3-{[(diethylamino)methyl]amino} quinazolin-4(3*H*)-one	$C_{17}H_{26}N_4O$	302.414	86.20%	Solid
A3	2-butyl-3-{[(diphenylamino)methyl]amino} quinazolin-4(3*H*)-one	$C_{21}H_{18}N_4O$	342.394	88.83%	Solid
A4	2-butyl-3-{[(phenylamino)methyl]amino} quinazolin-4(3*H*)-one	$C_{19}H_{22}N_4O$	322.404	84.23%	Solid
A5	3-({[(4-bromophenyl)amino]methyl}amino)-2-butylquinazolin-4(3*H*)-one	$C_{19}H_{21}BrN_4O$	401.300	81.21%	Solid

PHYSICAL DATA OF THE TITLED COMPOUND

Table No:1

Compound Code	Chemical Name	Molecular Formula	Molecular Weight(grams)	Percentage Yield	Appearance
A6	2-butyl-3-({[(4-nitrophenyl)amino]methyl} amino)quinazolin-4(3*H*)-one	$C_{19}H_{21}N_5O_3$	367.402	85.74%	Solid
A7	4-({[(2-butyl-4-oxoquinazolin-3(4*H*)-yl)amino]methyl}amino)benzoic acid	$C_{20}H_{22}N_4O_3$	366.414	83.01%	Solid
A8	4-({[(2-butyl-4-oxoquinazolin-3(4*H*)-yl)amino]methyl}amino)benzene Sulphonamide	$C_{19}H_{23}N_5O_3S$	401.483	75.75%	Solid
A9	2-butyl-3-[(1*H*-indol-1-ylmethyl)amino]quinazolin-4(3*H*)-one	$C_{21}H_{22}N_4O$	346.425	90.93%	Solid
A10	3-[(1*H*-benzotriazol-1-ylmethyl)amino]-2-butylquinazolin-4(3*H*)-one	$C_{19}H_{20}N_6O$	348.402	93.55%	Solid

MELTING POINT ANALYSIS

Melting point was found in an open end capillary tube method by electrically heating melting point apparatus.

The melting point of synthesized compounds is given in the Table No : 2

Table No: 2

S.NO	COMPOUND	MELTING POINT ^{0}C
1.	A1	206-209
2.	A2	148-152
3.	A3	226-230
4.	A4	241-243
5.	A5	272-275
6.	A6	255-258
7.	A7	236-239
8.	A8	278-282
9.	A9	222-227
10.	A10	229-234

THIN LAYER CHROMATOGRAPHY ANALYSIS

Thin layer chromatography analysis was carried out by using Silica gel G (0.5mm thickness) coated over glass plate (12x20cm) as stationary phase, Methanol: Chloroform: Water (8:1:1) as mobile phase, the spots were visualized by iodine vapours.

The Rf value of the synthesized compounds are given in the Table No: 3

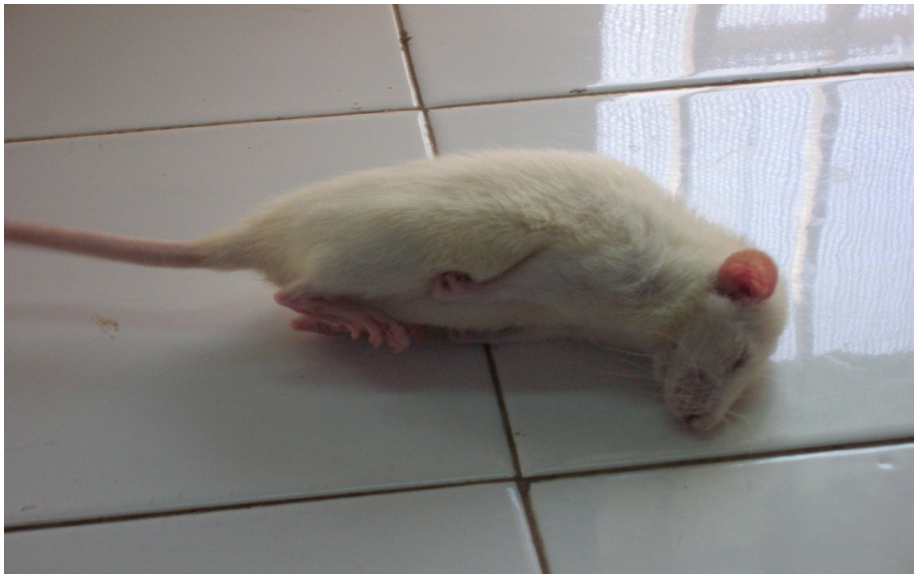
Table No: 3

S.No	COMPOUND	Rf VALUE
1.	A1	0.9459
2.	A2	0.8714
3.	A3	0.8472
4.	A4	0.8873
5.	A5	0.9054
6.	A6	0.8243
7.	A7	0.8667
8.	A8	0.9577
9.	A9	0.9305
10.	A10	0.8933

ANTI CONVULSANT ACTIVITY OF QUINAZOLINONE DERIVATIVES

ELECTRO CONVULSOMETER

ANTI CONVULSANT ACTIVITY OF QUINAZOLINONE DERIVATIVES



FLEXION PHASE

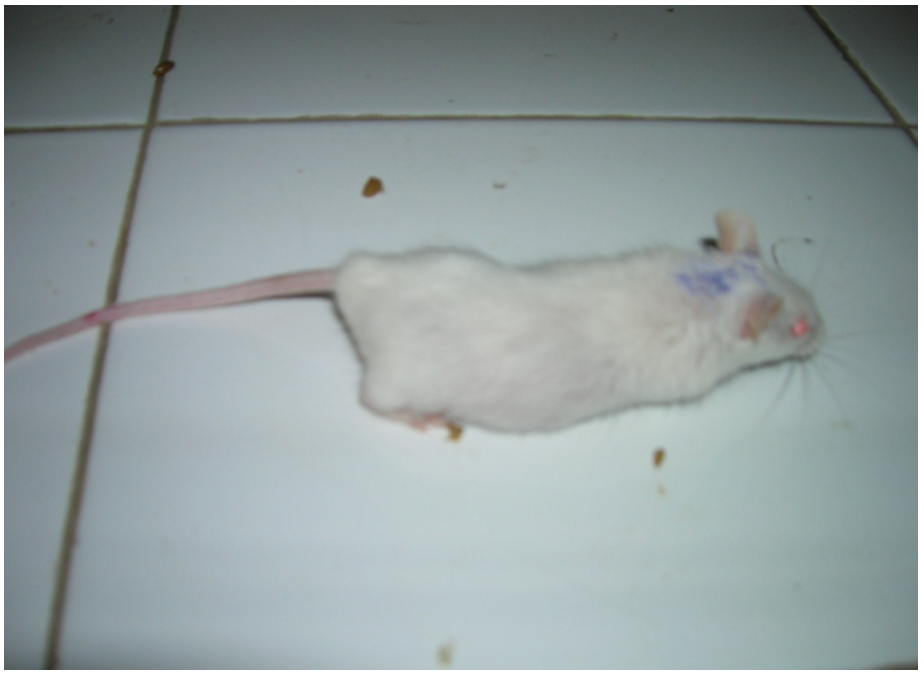
EXTENSOR PHASE

ANTI CONVULSANT ACTIVITY OF QUINAZOLINONE DERIVATIVES

CLONUS PHASE

STUPOR PHASE

ANALGESIC ACTIVITY OF QUINAZOLINONE DERIVATIVES



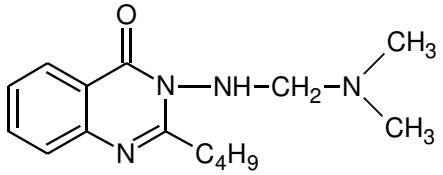
WRITHING EFFECT

INFRA RED SPECTRAL ANALYSIS [59-65]

The structure of the synthesized compounds was elucidated by PERKIN-ELMER FT-IR spectrophotometry using potassium bromide disc. The infra red values were measured as wave number in cm^{-1} and the results are shown below.

A-1

2- butyl-3-{[(dimethylamino)methyl]amino}quinazolin-4(3H)-one



IR Values:

3484.74 cm^{-1} - N-H Stretch (amine in side chain)

3025.34 cm^{-1} - C-H Stretch (in aromatic amine)

2925.26 cm^{-1} - C-H Stretch (in CH2 methylene bridge)

2869.56 cm^{-1} - C-H Stretch

1665.23 cm^{-1} - C=O Stretch

1510.95 cm^{-1} - C=N Stretch

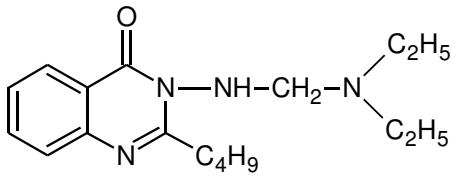
1450.22 cm^{-1} - C-H Bending

1035.59 cm^{-1} - C-C Stretch (in aliphatic ring)

1079.31 cm^{-1} - C-N Stretch

A-2

2- butyl -3- {[(diethylamino)methyl]amino}quinazolin-4(3H)-one



IR Values:

3450.17cm-1 - N-H Stretch (in side chain)

3080.33 cm-1 - C-H Stretch (C-H Stretching in Aromatic ring)

2928.65cm-1 - C-H Stretch

2885.93 cm-1 - C-H Stretch (C-H Stretching in CH3)

1641.13 cm-1 - C=O Stretch

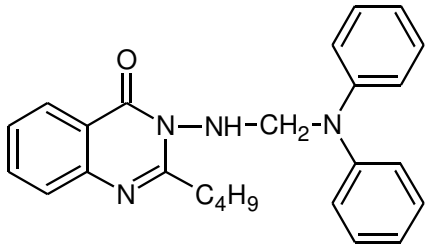
1590.32 cm-1 - C=N Stretch

1111.76 cm-1 - C-C Stretch

1059.22 cm-1 - C-N Stretch

A-3

2-butyl-3-{[(diphenylamino)methyl]amino}quinazolin-4(3H)-one



IR Values:

3339.17cm-1 - N-H Stretch (in side chain)

3050.67 cm-1 - C-H Stretch (C-H Stretching in Aromatic ring)

2932.47cm-1 - C-H Stretch

2888.76 cm-1 - C-H Stretch (C-H Stretching in CH3)

1663.66 cm-1 - C=O Stretch

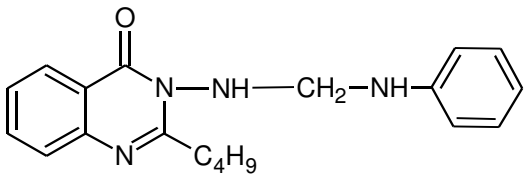
1592.94 cm-1 - C=N Stretch

1110.63 cm-1 - C-C Stretch

1050.53 cm-1 - C-N Stretch

A-4

2-butyl-3-{[(phenyl amino)methyl]amino}quinazolin-4(3H)-one



IR Values

3460.34 cm-1 - N-H Stretch (in side chain)

3055.33 cm-1 - C-H Stretch (C-H Stretching in Aromatic ring)

2933.39 cm-1 - C-H Stretch (CH_2)

2895.26 cm-1 - C-H Stretch (C-H Stretching in CH3)

1641.73 cm-1 - C=O Stretch

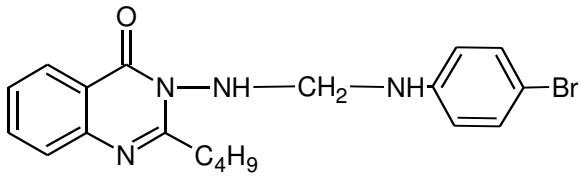
1596.12 cm-1 - C=N Stretch

1286.22 cm-1 - C-C Stretch

1120.11 cm-1 - C-N Stretch

A-5

3-({[(4-bromophenyl)amino]methyl}amino)-2-butylquinazolin-4(3H)-one



IR Values:

3429.33cm-1 - N-H Stretch (in side chain)

3020.12 cm-1 - C-H Stretch (C-H Stretching in Aromatic ring)

1495.67 cm^{-1} - C=C Stretch (in Aromatic ring)

2869.86cm-1 - C-H Stretch

2930.96 cm-1 - C-H Stretch (C-H Stretching in CH_2)

1655.74 cm-1 - C=O Stretch

1594.62 cm-1 - C=N Stretch

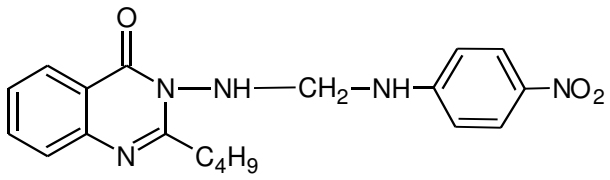
1249.26 cm-1 - C-C Stretch

1070.42 cm-1 - C-N Stretch (in side chain)

600.26 cm-1 - C-Br Stretch

A-6

2-butyl-3-({[4-nitrophenyl]methyl}amino)quinazolin-4(3H)-one



IR Values:

3447.13cm-1 - N-H Stretch (in side chain)

3080.33 cm-1 - C-H Stretch (C-H Stretching in Aromatic ring)

2885.93cm-1 - C-H Stretch

2930.96 cm-1 - C-H Stretch (C-H Stretching in CH_2)

1639.21 cm-1 - C=O Stretch

1598.32 cm-1 - C=N Stretch

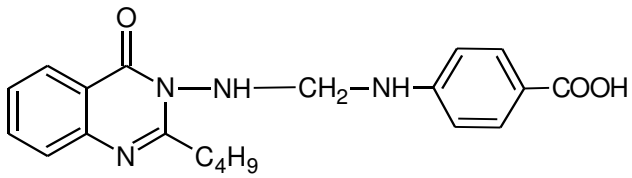
1111.76 cm-1 - C-C Stretch

1059.22 cm-1 - C-N Stretch (in side chain)

1535.67 cm^{-1} - N-O Stretch

A-7

4-({[(2-butyl-4-oxoquinazolin-3(4H)-yl)amino]methyl}amino)benzoic acid



IR Values:

3340.11cm^{-1} - N-H Stretch (in side chain)

3060.65 cm^{-1} - C-H Stretch (C-H Stretching in Aromatic ring)

2889.34cm^{-1} - C-H Stretch

2932.31 cm^{-1} - C-H Stretch (C-H Stretching in CH_2)

1634.38 cm^{-1} - C=O Stretch

1570.23 cm^{-1} - C=N Stretch

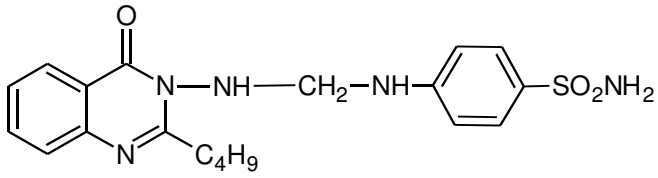
1116.58cm^{-1} - C-C Stretch

1044.45 cm^{-1} - C-N Stretch (in side chain)

2690.97 cm^{-1} - COOH Stretch

A-8

4-({[(4-oxoquinazolin-3-(4H)-yl) amino]methyl}amino)benzene sulphonamide



IR Values:

3305.69 cm^{-1} - N-H Stretch (in SO_2NH_2)

2860.43 cm^{-1} - C-H Stretch in CH_3

2924.12 cm^{-1} - C-H Stretch (C-H Stretching in CH_2)

1660.23 cm^{-1} - C=O Stretch

1580.11 cm^{-1} - C=N Stretch

1103.34 cm^{-1} - C-C Stretch

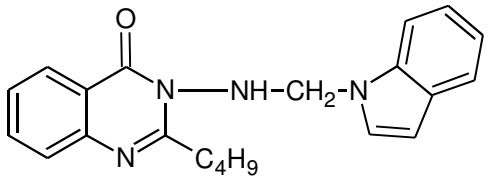
1050.41 cm^{-1} - C-N Stretch (in side chain)

901.11 cm^{-1} - S-N Stretch

1370.56 cm^{-1} - SO_2 Stretch

A-9

2-butyl-3-[(1H-Indol-1-yl methyl)amino]quinazolin-4(3H)-one



IR Values:

3500.12cm^{-1} - N-H Stretch (sharp)

3065.53cm^{-1} - C-H Stretch (C-H Stretching in Aromatic ring)

2857.63cm^{-1} - C-H Stretch

2930.06 cm^{-1} - C-H Stretch (C-H Stretching in CH_2)

1639.21 cm^{-1} - C=O Stretch

1563.63 cm^{-1} - C=N Stretch

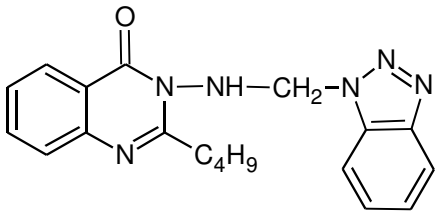
1124.33cm^{-1} - C-C Stretch

1060.19 cm^{-1} - C-N Stretch (in side chain)

2690.97 cm^{-1} - COOH Stretch

A-10

3-[(1*H*-benzotriazol-1-ylmethyl)amino]-2-butylquinazolin-4(3*H*)-one



IR Values:

3491.17cm^{-1} - N-H Stretch (sharp)

3050.41cm^{-1} - C-H Stretch (C-H Stretching in Aromatic ring)

2865.78cm^{-1} - C-H Stretch

2931.12 cm^{-1} - C-H Stretch (C-H Stretching in CH_2)

1654.38 cm^{-1} - C=O Stretch

1598.26 cm^{-1} - C=N Stretch

1110.82cm^{-1} - C-C Stretch

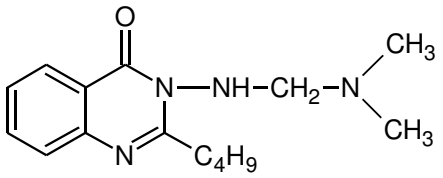
1069.91 cm^{-1} - C-N Stretch (in side chain)

3300.22 cm^{-1} - N-N Stretch

NUCLEAR MAGNETIC RESONANCE SPECTRAL ANALYSIS [60, 63, 64]

The structures of the synthesized compounds were elucidated by BRUCKER 300 MHz FT- NMR using TMS (Tetramethyl Silane) as internal standard. The Proton Magnetic Resonance Spectroscopic values are measured in δ ppm in $CDCl_3$.

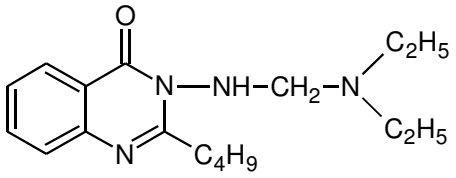
Sample A1



2-butyl-3-{[(dimethyl amino) methyl] amino}quinazolin-4(3*H*)-one

1.2782	-	t,	2H,	C_4H_9	
2.2564	-	s,	6H,	$N(CH_3)_2$	
7.5602	-	t,	1H,	C_6-H	of Quinazolinone moiety.
7.3385	-	t,	1H,	C_7-H	
8.0370	-	d,	1H,	C_5-H	
8.0523	-	d,	1H,	C_8-H	

Sample A2

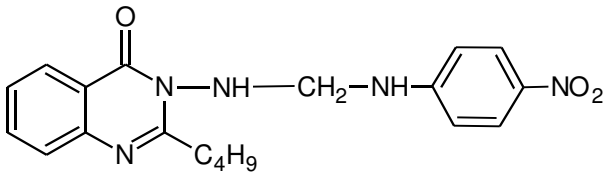


2-butyl-3-{[(diethylamino)methyl]amino}quinazolin-4(3*H*)-one

1.2446	-	s,	10H,	$N(C_2H_5)_2$	
2.3772	-	t,	2H,	C_4H_9	

7.600	-	t,	1H,	C_6-H	
7.1245	-	t,	1H,	C_7-H	of Quinazolinone
8.7050	-	d,	1H,	C_5-H	moiety.
8.1333	-	d,	1H,	C_8-H	

Sample A6

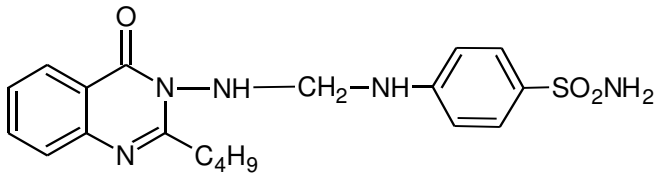


2-butyl-3-({[(4-nitrophenyl)amino]methyl}amino)quinazolin-4(3*H*)-one

2.4169	-	t,	2H,	C_4H_9	
7.8000-8.0150	-	m,	4H,	Ar-H	

7.1444	-	d,	1H, C_5-H	
7.5112	-	t,	1H, C_6-H	of Quinazolinone
8.0156	-	t,	1H, C_7-H	moiety.
8.9709	-	d,	1H, C_8-H	

Sample A8

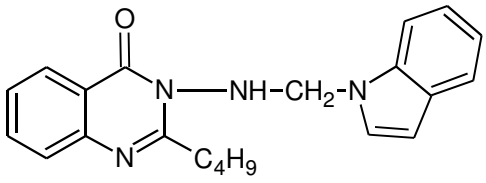


4 -({[(2 -butyl -4 -oxoquinazolin -3(4H) -yl)amino]methyl}amino)benzene sulphonar

3.042	-	t,	2H,	C_4H_9

7.398-7.791	-	m,	4H,	Ar-H	
7.830	-	t,	1H,	C_7-H	of Quinazolinone moiety.
8.313	-	t,	1H,	C_6-H	
8.378	-	d,	1H,	C_8-H	
8.7000	-	d,	1H,	C_5-H	

Sample A9



2-butyl-3-[(1*H*-indol-1-ylmethyl)amino]quinazolin-4(3*H*)-one

1.2000	-	t,	2H,	C_4H_9	
7.5-7.6	-	m,	4H,	Ar-H	
6.969	-	t,	1H,	C_7-H	of Quinazolinone moiety.
7.367	-	t,	1H,	C_6-H	
8.224	-	d,	1H,	C_5-H	
8.250	-	d,	1H,	C_8-H	

ANTI CONVULSANT ACTIVITY [66-70]

INTRODUCTION

Anti convulsant drugs are intended for the treatment of convulsive disorders in man. Convulsions may arise due to many reasons most of the animal techniques used for evaluating anti – epileptic drugs.

The general principle is to produce seizures by electrical stimulation as by systemic administration of convulsant chemical agent. Eg: pentylene tetrazole or production of a chronic, focal epileptogenic lesion.

By electrical stimulation of the brain a variety of seizers can be produced.

The principle being,

a) Supra maximal electrical shock
b) Psychomotor electrical shock
c) Minimal electrical shock

SUPRA MAXIMAL ELECTRICAL METHOD

The electro shock assay in rat is used primarily as an indication for compounds which are effective in grandmal epilepsy.

Male albino wistar rats are stimulated through are stimulated through pinna electrodes (150 mA – alternating current, 0.2 sec – stimulus duration)

The resultant seizure in normal rats shows a tonic phase of limb flexion around 2 seconds, followed by full tonic extension phase around 10 -13 seconds and a few clonic jerks there after the number of post – tonic as physical death are noted.

REQUIREMENTS:

Animal: Male albino wistar rats (200 – 250 g)

Drugs: standard (Phenytoin sodium (25 mg / kg))

Test: Synthetic drugs (5 mg / kg)

Instrument: Electro convulsiometer model, Ki – 9531

PROCEDURE:

1. Healthy albino wistar rats weighing from 200 – 250 g were selected. They were kept in separate cages, fed with balanced diet, water and libitum
2. Then the animals were divided into 12 groups each groups containing four animals.
3. The first groups of animals were served as control, which received 0.5 ml DMSO.
4. Second group served as standard which received phenytoin sodium (25 mg/kg)
5. Third group treated with C2 compound (5 mg/kg)
6. Fourth group treated with C5 compound (5 mg/kg)
7. Fifth group treated with C6 compound (5 mg/kg)
8. Sixth group treated with C7 compound (5 mg/kg)
9. Seventh group treated with C8 compound (5 mg/kg)
10. Eighth group treated with C9 compound (5 mg/kg)
11. Ninth group treated with C1 compound (5 mg/kg)
12. Tenth group treated with C3 compound (5 mg/kg)
13. Eleventh group treated with C4 compound (5 mg/kg)
14. Twelfth group treated with C10 compound (5 mg/kg)

All the test compounds were dissolved in solvent like DMSO and administered through intra-peritoneal route.

The evaluation was started 30 mins after administration of test compounds. Pinna electrodes with the intensity of 150 mA current were used to deliver the stimuli.

Inhibition of seizure relative to the control was calculated and the data shown on the table.

ANTI CONVULSANT ACTIVITY OF VARIOUS SYNTHESIZED DRUGS BY SUPRA MAXIMAL ELECTRICAL SHOCK METHOD

Table No: 4

Treatment	Body Wt.	Drug	Dose	Duration of extension phase in seconds	% inhibition of extension phase
Group I	180 – 200 gm	Normal saline	10 ml / kg	13.52 ± 0.12	------
Group II	180 – 200 gm	Phenytoin sodium	25 mg / kg	2.5 ± 0.20	81.50 %
Group III	180 – 200 gm	A1	5 mg / kg	6.25 ±. 0.32	53.77 %
Group IV	180 – 200 gm	A2	5mg/ kg	4.12 ± 0.31	69.52 %*a
Group V	180 – 200 gm	A3	5 mg / kg	6.85 ±. 0.28	49.33 %
Group VI	180 – 200 gm	A4	5 mg / kg	7.02 ±. 0.33	48.08 %
Group VII	180 – 200 gm	A5	5 mg/ kg	4.20 ± .0.45	68.93 %*a
Group VIII	180 – 200 gm	A6	5 mg / kg	4.35 ± 0.55	67.82 %*a
Group IX	180 – 200 gm	A7	5 mg / kg	4.22 ± 0.40	68.78 %*a
Group X	180 – 200 gm	A8	5 mg / kg	4.02 ±. 0.35	70.26 %*a
Group XI	180 – 200 gm	A9	5 mg / kg	3.99 ±. 0.28	70.48 %*a
Group XII	180 – 200 gm	A10	5 mg / kg	6.55 ±. 0.28	51.55 %

- values are expressed as Mean ± SEM
- values are find out by using One way ANOVA followed by Newman Keul's multiple range test.

*a *a Values are significantly different from normal control at P<0.01.

ANALGESIC ACTIVITY [69-72]

EVALUATION OF ANALGESIC ACTIVITY

The analgesic activities of various synthesized compounds were screened by using acetic acid induced writhing test in mice. Mice of either sex weighing between 20 –25 gm were taken in12 groups of each 4 animals.

Diclofenac sodium 10mg/kg was used as a standard drug for comparison of analgesic activity. Writhing was induced by administration 0.2ml of 1%v/v of aceticacid through intraperitoneally. Record the number of abdominal contractions,trunk twist response and extension of hind limbs as well as the number of animals showing such response during a period of 25 min.

Administer all synthesized compound through I.P.Half an hour later adminiser aceticacid solution at 1ml/100gm B.W. Note and calculate onset and severity of writhing response. Note the inhibition of pain response by synthesized drugs.

EFFECT OF ANALGESIC ACTIVITIES OF SYNTHESIZED COMPOUNDS AGAINST ACETIC ACID INDUCED WRITHING TESTS IN MICE.

Table No: 5

GROUP	COMPD	DOSE	NO FO WRITHES IN 25MIN(Mean ± SEM)	%INHIBITION
G1(Normal control)	Normal saline	10 ml / kg	27.90±.0.40	-----
G2 (STD)	Diclofenac sodium	10 mg / kg	7.45±0.62.	73.29%
G3(Treatment control)	A1	5 mg / kg	8.95±0.72	67.92%*a
G4	A2	5mg/ kg	8.58±0.45	69.24%*a
G5	A3	5 mg / kg	13.54±1.65	51.46%
G6	A4	5 mg / kg	13.5±1.25	51.61%
G7	A5	5 mg/ kg	8.22±0.52	70.53%*a
G8	A6	5 mg / kg	12.70 ±1.33	54.48%
G9	A7	5 mg / kg	12.85±1.22	53.94%
G10	A8	5 mg / kg	8.50±0.74	69.53%*a
G11	A9	5 mg / kg	8.62±0.45	69.10%*a
G12	A10	5 mg / kg	8.83±0.76	68.35%*a

- values are expressed as Mean ± SEM

- values are find out by using One way ANOVA followed by Newman Keul's multiple range test.

*a Values are significantly different from normal control at P<0.01.

RESULTS AND DISCUSSION

SYNTHETIC METHODOLOGY:

The titled compounds were synthesized in a 3 step process:

- The first step in which Anthranilic acid undergoes **cyclization** by the treatment with Pentanoic anhydride to yield 2-butyl-4H-3, 1-benzoxazin-4-one.
- The advantage is that it is an useful intermediate to afford 3-amino-2(n-butyl)-quinazolin-(3H)-4one on **condensation with Hydrazine hydrate**.
- The presence of active hydrogen in **N-3 position** facilitates the **Mannich reaction** to take place with several amines to yield 3-substituted amino-2(n-butyl)quinazolin-(3H)-4-one derivatives.

Characterization:

- The **melting points** were found in an open end capillary tube method by electrically heating melting point apparatus and are uncorrected.
- The purity of the compounds were analysed by **Thin Layer chromatography** using Silica Gel (0.5 mm thickness) as stationary phase, employing Methanol:Chloroform:Water (9:1:1) as Mobile phase, spots were visualized using Iodine vapours.

  The Rf value of the synthesized compounds were calculated.

- The characterization of the titled compounds including **Infrared and Nuclear Magnetic Resonance Spectral data** were in correlation with the expected structure.

PHARMACOLOGICAL SCREENING:

Anti Convulsant Activity:

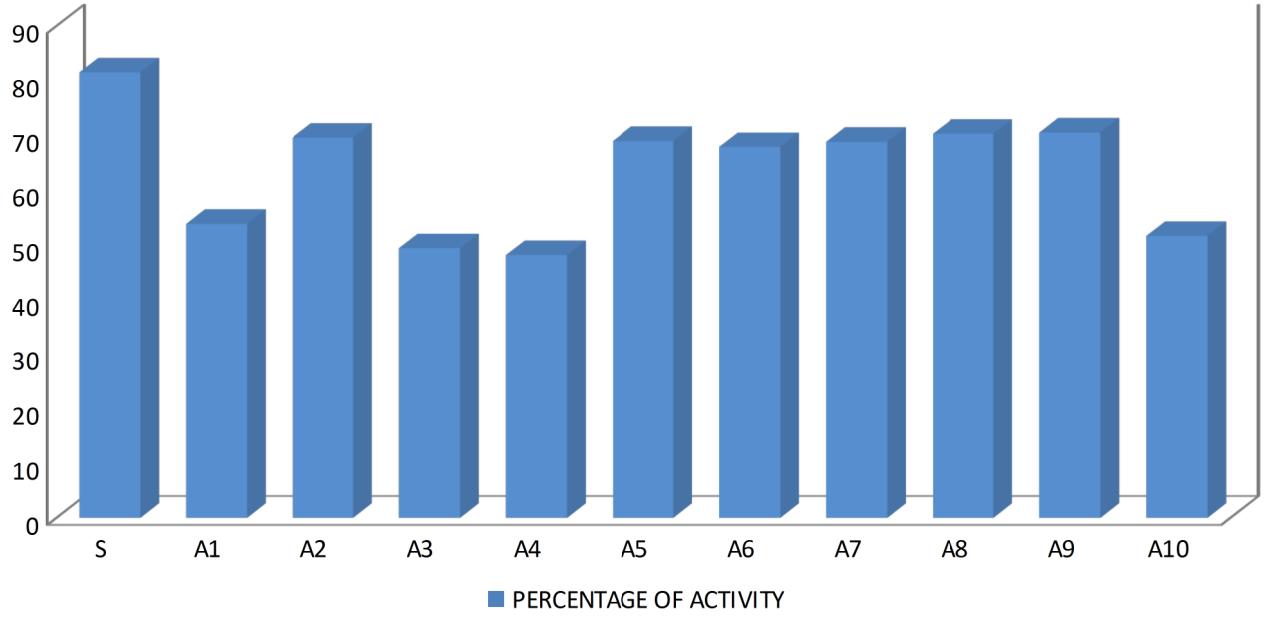
- Anti Convulsant activity of the synthesized compounds were evaluated by **Supra Maximal Electrical Shock Method**, because it was the most widely employed seizure models for the early identification and high throughput screening of investigational Antiepileptic Drugs.
- Compounds **A2, A5,A6,A7,A8 and A9** (5mg/Kg) abolished the duration of extensor phase when compared to the control and hence they were concluded to possess **significant Anticonvulsant Activity.**
- The standard drug **Phenytoin sodium** at a dose of 25mg/kg produced drastic abolision of **extensor phase.**
- Compounds like A1,A3,A4 and A10(5mg/kg) does not possess significant Anticonvulsant activity when compared to control(Standard Group)

Analgesic Activity:

- The synthesized compounds were evaluated for Analgesic Activity by **Acetic acid Induced Writhing Method.**
- Maximum degree of Analgesic Activity was observed for compounds **A1, A2, A5, A8, A9 andA10**(5mg/kg)**.** The writhing effect was significantly inhibited by the above compounds
- The standard drug **Diclofenac Sodium** at a dose of 10mg/kg inhibited the writhing effect to a greater extent.
- Compounds like A3, A4, A6 and A7(5mg/kg) possess moderate analgesic activity when compared to standard group.

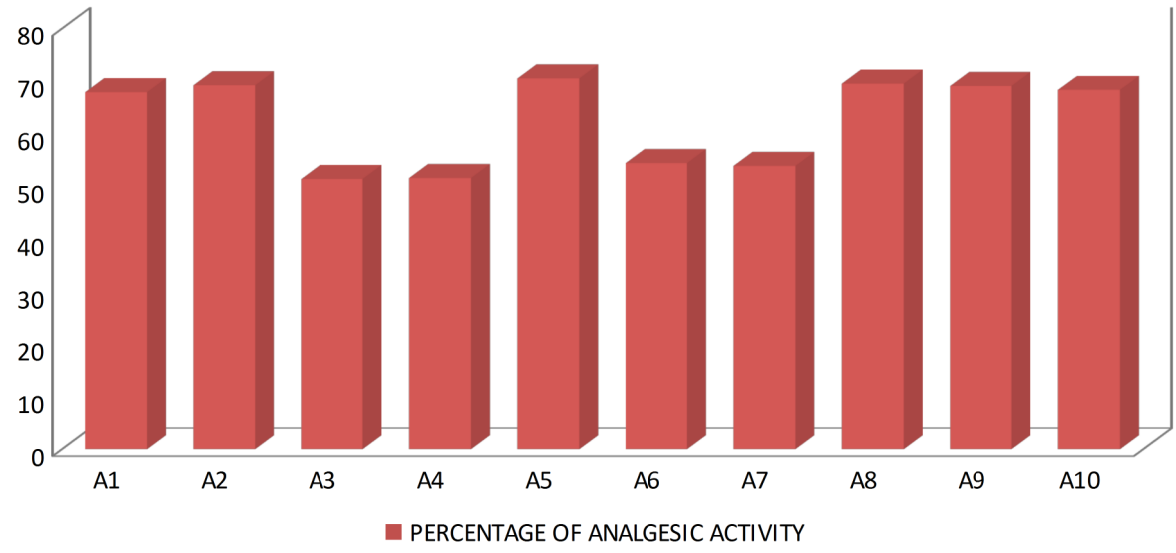
ANTI CONVULSANT ACTIVITY OF VARIOUS SYNTHESIZED DRUGS BY SUPRA MAXIMAL ELECTRICAL SHOCK METHOD

Chart No: I



EFFECT OF ANALGESIC ACTIVITIES OF SYNTHESIZED COMPOUNDS AGAINST ACETIC ACID INDUCED WRITHING TESTS IN MICE.

Chart No: II



CONCLUSION

- **Novel 2-(n-butyl)-3-substituted amino Quinazolin-4(3H)-ones** were synthesized by a 3step process using Anthranilic acid and Pentanoic anhydride as starting materials.

- The **Melting points** were found for the synthesized compounds and are uncorrected. The purity of the synthesized compounds were analysed by **Thin Layer Chromatography methods.**

- The structures of the synthesized compounds has been elucidated by **Infrared and Nuclear Magnetic Resonance Spectroscopy.**

- The **anticonvulsant activity** of the synthesized compounds (5mg/kg) were screened by **Supra Maximal Electrical Shock method** in Albino Rats against the standard drug Phenytoin (25mg/kg)

- The result obtained showed that the attachments of **diethyl amine,4-bromo aniline,**

  4-nitro aniline, P-Amino benzoic Acid, Sulphanilamide and Indole moieties to the Quinazolin- 4(3H)-one ring exhibited **significant Anticonvulsant activity**.

- Based on the results, the attachment of **dimethyl amine, benztriazole to Quinazolin-4(3H)-on**e shown to have **moderate Anticonvulsant activity** while **diphenyl amine, aniline substituted Quinazolin-4(3H)-one** shown to have **less Anticonvulsant activity** comparatively.

- The **analgesic activity** of the synthesized compounds (5mg/kg) were screened by **Acetic Acid Induced Writhing metho**d in Albino rats against the standard drug Diclofenac sodium(25mg/kg)

- From the obtained results **Quinazolin-4(3H)-one** ring having substitutions like Dimethyl amine, diethyl amine, 4-bromoaniline,sulphanilamide,Indole Benztriazole showed **significant Analgesic Activity** while the other groups shows only Moderate Activity.

- Future investigations can be made to study its **Pharmacokinetic parameters**, **potency,efficacy, drug interactions ,side effects of the titled compounds** in order to bring out the novel Quinazoline -4(3H)-one derivatives as a successful drug molecules.

- Extended studies can be made to broaden the therapeutic utility of the synthesized compounds **such as anti microbial, anti malarial, anti tuberculosis, anti parkinsonism, anti HIV, anti cancer, anti histaminic, local anaesthetic, anti hypertensive and antiviral activities**

BIBLIOGRAPHY

1. **Alfred Burger' s Medicinal Chemistry**, Third Edition, 1970 part-I Wiley-Interscience publishers, NewYork, pp.1

2. **Wilson and Gisvold's Text book of Organic Medicinal and Pharmaceutical Chemistry**, 10th edition,1998, Lippincott Williams and Wilkins,Philadelpia pp. 1, 3.

3. **Remington; The Science And Practice of Pharmacy**; twentieth Edition; 2000, Vol-I Lippincott Williams & Wilkin's, Philadelpia, pp.458

4. **Text Book Of Drug Design And Discovery**, PovlKrogs gaard Larsen, Tommy liljefors and Ulfmadsen Taylor and Francis, pp. 1.

5. **Comprehensive Medicinal Chemistry, The Rational Design, Mechanistic study and Therapeutic applications of chemical compound**, vol- I Pergamon Press, pp.4.

6. **Heterocyclic Chemistry, Synthesis, Reactions & Mechanisms**, Raj.K.Bansal, Wiley Eastern Ltd., pp.375.

7. Usha Ameta, Swati Ojha**,** Synthetic studies on some 3-[(5-arylidene-4-oxo-1,3-thiazolidin-2 yliden)amino]-2-phenylquinazolin-4(3*H*)-ones and their ethoxyphthalimide derivatives, **ARKIVOC 2006** , Vol (xiii), pp .83-89

8. Murugesan Dinakaran,Periyaswamy Selvam, Eric Declercq and Seshaiah Krishnan Sridhar, Synthesis, Antiviral and Cytotoxic Activity of 6-Bromo-2,3-disubstituted-4(3*H*)-quinazolinones **Biol.Pharm.Bull. 2003**, Vol 26 no 9, pp.1278-1282

9. Veerachamy Alagarsamy, Durairaj Shankar, Viswas Raja Solomon, Rajendra Vasant Sheorey and Periyasamy Parthiban, **Acta Pharm. 59, 2009**, Pp.75-88

10. A.M.F. Eissa, A.M. EI.Metwally, M. A. El-hashash and A. M. F. El-gohary, **Journal of the Korean Chemical Society,2008,** Vol .52, No.3, pp.328-337

11. Veerachamy Alagarsamy, Kunchu Kavitha, Mani Rupeshkumar, Viswas Raja Solomon Jaya Kumar, Dinakaran Sathesh Kumar and Hemant Kumar Sharma, **Acta Pharm, 2009,** 59, pp. 97-106

12. Veerachamy Alagarsamy, Viswas Raja Salomon, Gnanavel Vanikavitha, Veeran Paluchamy, Muniyandi Ravi Chandran, Augustin Arnald Sujin, Arunachalam Thangathiruppathy, Sivaperuman Amuthalakshmi, and Rajappan Revathi, **Biol. Pharm. Bull, 2002**, Vol-25, No: 11, pp. 1432-1435

13. Veerachamy Alagarsamy, Veluchamy MuthuKumar, Nagendran Pavalarani, Poongavanam Vasanthanathan and Rajappan Revathi **Biol. Pharm. Bull, 2003,** Vol-26, No: 4, pp. 557-559

14. Veerachamy Alagarsamy, Ramadoss Rajesh, Meena Ramaseshu, Sukumaran Vijaykumar, Kona Venkat Ramseshu and Thirumoorthy Duraianandakumar, **Biol. Pharm. Bull, 2004,** Vol-27, No: 5, pp. 652-656

15. V. Alagarsamy, R. Giridhar, M.R. Yadav, R. Revathi, K. Ruckmani, and E. DE Clercq **Indian J. Pharm. Sci., 2006,** 68 (4), pp. 532-535

16. Veerachamy Alagarsamy and Sankaranarayanan Murugesh **Chem. Pharm. Bull., 2007,** Vol-55, No-1, pp. 76-80

17. Usha Ameta, Swati ojha, Dinesh Bhambi and Ganpat L. Talesara **ARKIVOC 2006,** (xiii), pp. 83-89

18. Veerachamy Alagarsamy, Rajani Giridhar and Mangae Ram Yadav, **Biol. Pharm. Bull**., **2005**, Vol-28, No-8, pp.1531-1534

19. Veerachamy Alagarsamy, Viswas Raja Salomon, Ramseshu Meena and Kona Venkat Ramseshu **Biol. Pharm. Bull., 2005,** Vol-28, No-6, pp.1091-1094

20. Vinod K. Tiwari, Raju R. Kale, Bhuwan B. Mishra, and Archana Singh, **ARKIVOC 2008**, (XIV), pp. 27-36

21. P. ManiChandrika, T. Yakaiah, B. Narsaiah, V. Sridhar, G. Venugopal, J. Venkateswara Rao, K. Pranay Kumar, U S N Murthy and A. Raghu Ram Rao, **Indian Journal of Chemistry, 2009**, Vol-48B, pp.840-847

22. M.B Raju, S.D. Singh, A. Raghu Ram Rao, and K. S. Rajan, **Indian J. Pharm. Sci., 2007**, 69 (6), pp.853-856

23. E.M. Jessy, A. Thirugnana Sambanthan, J. Alex, C.H. Sridevi, and K.K. Srinivasan **Indian J. Pharm. Sci., 2007,** 69(3), pp. 476-478

24. L. Cipak, A. Repicky, S. Jantova, **Exp Oncol 2007,** 29,1, pp. 13-17

25. Maykel Cruz- Monteagudo, Fernanda Borges, M. Natalia D. S. Cordeiro, **ECSOC-12, 2008**, pp. 1-30

26. N.M. Raghavendra, P.P.Thampi and P.M. Gurubasavarajaswamy, **E Journal of Chemistry**, January **2008**, Vol.5, No.1, pp.23-33

27. Chang Xie, Nian-Yu Huang and Ming-Wu Ding, **ARKIVOC 2009**, (X), pp.220-232

28. Sachin S. Laddha, Sudhir G. Wadodkar and Sharad K. Meghal, **ARKIVOC 2006**, (xi), pp.1-20

29. Veerachamy Alagarsamy, Durairaj Shankar, Muthuvel Murugan, Anees Ahmed Siddiqui, and Ramadoss Rajesh, **Arch. Pharm. Chem. Life Sci. 2007**, 340, pp.41-46

30. Periyasamy Selvam, K. Babu, R. Padamraj, Leentje persoons and Erik de Clercq, **African Journal of Pharmacy and Pharmacology, 2008**, Vol.2, (6), pp.110-115

31. V. Alagarsamy, S. Murugesan, R.V. Sheorey, **Med Chem Res, 2008**, 17, pp.564-577

32. N.M. Raghavendra, M.S.Niranjan, P.Venkatesh, B.R.Prashantha Kumar, Narendra B.Gowda, M.S.Sripathi, **Asian Journal of Chemistry, 2005**, Vol.17, No.1, pp.57-65

33. Mohamed A Abdo, Ibrahim F Zeid, Gamal A El-Miti, Olfat E Malmoud, **Indian Journal of Chemistry, 1999**, Vol.38 B, pp.850-853.

34. Anil K. Sengupta, Tapas Bhattacharya, **Journal of Indian Chemistry Society, 1983**, Vol IX, pp.373-376

35. S. Dev Singh, M. Bhagavan Raju, Rajesh H Bahekar, K.S. Rajan, A. Raghu Ram Rao, **Indian Journal of Chemistry, 2001**, Vol. 40B, pp.813-816

36. P. Selvam, K.Girija, R. Nagarajan, E. De Clercq, V. Gopal, **Indian Journal of Heterocyclic Chemistry, 2005**, 14, pp.255-256

37. R. K. Kawadkar, B. J. Ghiya, **Asian Journal of Chemistry, 1999**, Vol.11, No.2, pp.388-391

38. Pradeep Mishra, P. Paneerselvam, Sandeep Jain, **Journal of Indian Chemistry Society, 1995,**Vol.72, pp.559-560

39. V. Malla Ready, V. Murugan, Apsara, K.P. Kumar, B. Suresh, **Indian Journal of Heterocyclic Chemistry, 2004,** Vol.14, pp.67-68

40. V. Murugan, Caroline C. Thomas, G.V.S. Ramasarma, E.P. Kumar, B. Suresh, **Indian Journal of Pharmaceutical Sciences, 2003**, 65 (4), pp.386-389

41. N.B. Patel, J.D. Lilakar, **Indian Journal of Heterocyclic Chemistry, 2001**, Vol.11, pp.85-86

42. Ashok Kumar, V.K. Srivastava, Preeti Rani, Archana, **Indian Journal of Chemistry, 2002**, Vol.41 B, pp.2642-2646

43. Ashok Kumar, Mirdula Tyagi, V.K. Srivastava, **Indian Journal of Chemistry, 2003**, Vol.42 B, pp.2142-2145

44. P.C. Sarkar, S. Kumar, A.K. Shrivastava**, Indian Journal of Heterocyclic Chemistry, 1997**, Vol.7, pp.51-54

45. Bernard Pirotte, Fabin Somers, Raogo Ouedraogo, Marie-Helene Antoine, Pascal de Tullio, Benedicte Becker, Jeanine Fontaine, Jacques Damas, Leon Dupont, Benoit Rigo, Jacques Delarge, Philippe Leburn, **Journal of Medicinal Chemistry, 2001**, 44, pp.2575-2585

46. P.S.N. Reddy, P. Pratap Reddy, T. Vasantha, **Indian Journal of Chemistry, 2002**, Vol.41 B, pp.1946-1949

47. H.M.F. Madkour, **Arkat- USA**, Inc.

48. V. Alagarsamy, A. ThangaThiruppathy, S.c. Mandal, S. Rajasekaran, S. Vijaykumar, R. Revathi, J. Anburaj, S. Arunkumar, S. Rajesh, **Indian J. Pharm. Sci., 2006**, 68(1), pp. 108-111

49. V. Alagarsamy, S.Murugesan, K.Dhanabal, M. Murugan, E De Clercq, **Indian J. Pharm. Sci., 2007**, 69(2), pp. 304-307

50. Ahmad R. Khosropour, Iraj Mohammadpoor-Baltorka and Hamid Ghorbankhani, **Tetrahedron Letters ,2006,** 47,pp. 3561–3564

51. Tsuyoshi Nagase, Takashi Mizutani, Etsuko Sekino, Shiho Ishikawa, Sayaka Ito, Yuko Mitobe, Yasuhisa Miyamoto, Ryo Yoshimoto, Takeshi Tanaka, Akane Ishihara, Norihiro Takenaga, Shigeru Tokita, and Nagaaki Sato**,** ***J. Med. Chem.*** **2008,** *51,* pp. 6889–6901

52. Joachim Rudolph, William P. Esler, Stephen O'Connor, Philip D. G. Coish, Philip L,

J. Med. Chem. **2007,** *50,* pp. 5202-5216

53. Hirohiko Hasegawa,a, Masami Muraoka,a Kazuki Matsuia and Atsuyuki Kojimab, **Bioorg. Med. Chem. Lett., 2003,** 13, pp. 3471–3475

54. Yong Ho Na, Sung Ho Hong, Jung Hyang Lee, Woo-Kyu Park, Du-Jong Baek, Hun Yeong Koh, Yong Seo Cho, Hyunah Chooa, and Ae Nim Paea, **Bioorg. Med. Chem., 2008,** 16, pp. 2570–2578.

55. Bentley and Driver's Textbook of Pharmaceutical Chemistry, 8th Edition, Oxford University Press, pp. 613-614

56. Arun Bahl, B.S. Bahl, AdvancedOrganic Chemistry, S.Chand & Company ltd., 2005, pp.1088.

57. O.P. Agrawal, **Organic Chemistry, Reactions and Reagents**, Goel publishing house, Meerut, 44TH Edition, 2008, pp. 804-809

58. Jerry March, Advanced Organic Chemistry, Reactions, Mechanisms and Structure, 2nd Edition, McGraw Hill, pp. 900

59. Paula Yurkanis Bruice, Organic Chemistry,3rd Edition,2008, Pearson Education, pp. 497-500

60. Y.R. Sharma, Elementary organic Spectroscopy, Principles and Chemical Applications, 4th Edition, 2007, pp. 90-133, 223-230

61. B.K. Sharma, Instrumental Methods of Chemical Analysis, 24th Edition, 2005, Goel Publishing House, Meerut, pp.280-314

62. A.H. Beckett, J.B. Stenlake, Practical Pharmaceutical Chemistry, Part-II 4thedition, 2002, CBS Publishers & Distributors, New Delhi, pp.383-390

63. B.S. Furnis, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogel's Text book of Practical Organic Chemistry , 5th Edition, Person Education, first Indian Reprint 2004, New Delhi, pp. 1413-1422, 1424-1427

64. Robert .M. Silverstein, G. Clayton Bassler, Spectrophotometric Identification of Organic Compounds 2nd Edition, John Wiley & Sons, pp. 72-107, 120-135

65. Gurdeep R. Chatwal, Sham K.Anand,Instrumental Methods of Chemical Analysis, Himalaya Publishing House, 2003, pp.2.62-2.63

66. James E.P. Toman, Ewart. A. Swinyard and Louis. S. Goodman, Properties of maximal seizures and their alteration by anti Convulsant drugs and other agents **J. Neurophysiol., 1946,** 9, pp.231-239

67. A. Rajasekaran, R. Valarmathi, b. Jaykar, **Indian drugs .,** 33(12), pp. 617-618

68. S.K. Kulkarni, Hand book of Experimental Pharmacology, 3rd edition, Vallabh prakashan 2003, pp.131-133

69. Good man & Gilman's The Pharmacological Basis of Therapeutics, 10th Editon, McGraw Hill, pp. 521-531, 709-710

70. K.D. Tripathi, **Essentials of Medical Pharmacology**, 5th Edition, Jaypee Brothers Medical Publishers, pp. 167-178, 369-373

71. Shastrikant, V.Bhandari, Kailash G. Bothara, Mayuresh k. Raut, Ajit A. Patil, Aniket P. sarkate, Vinod J. Mokale, Design, Synthesis and evaluation of Anti-inflammatory, Analgesic and Ulcerogenicity studies of Novel 5-substituted phenacyl-1,3,4-Oxadiazole-2-thiol and Schiff bases of Diclofenac acid as non Ulcerogenic derivatives, **Bioorganic & Medicinal Chemistry, 2008,**16, pp.1822-1831

72. Mohammed Amir, Shikha kumar, Synthesis and evaluation of Anti-inflammatory, Analgesic, Ulcerogenic and Lipid peroxidation properties of Ibuprofen derivatives, **Acta Pharm, 2007**, 57,pp.31-45